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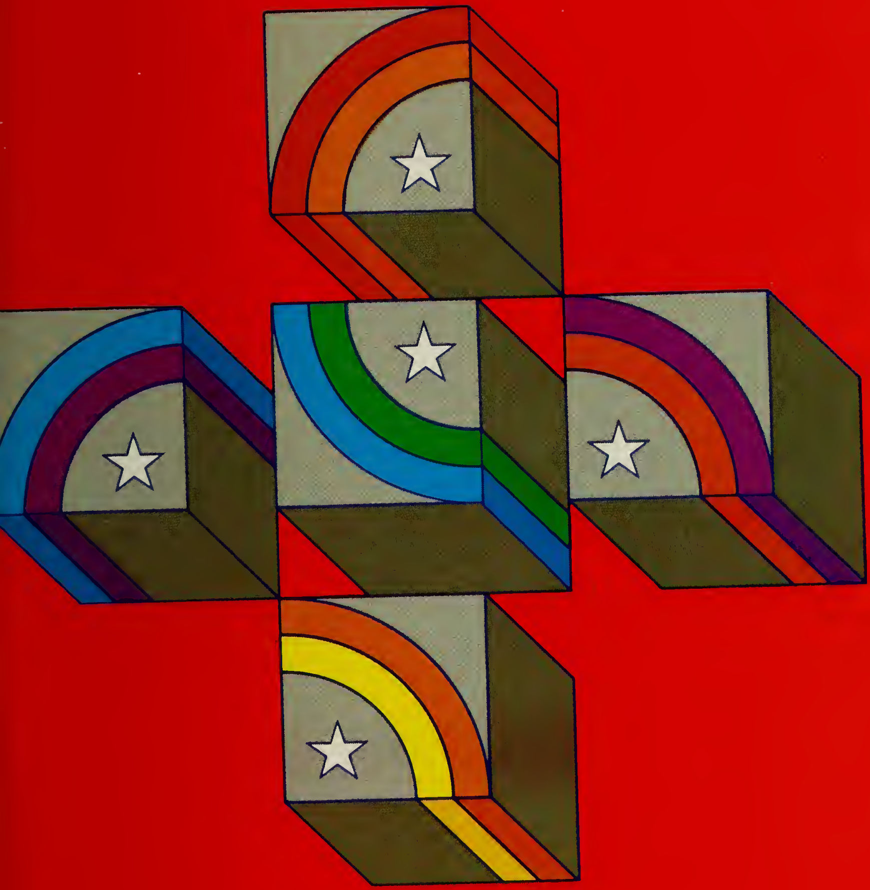

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DEPARTMENT
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1982

November 15, 1982	**Deadline for receipt of completed NIH Medical Staff Fellow applications**
January 10-21, 1983	**Interview period**
February 1-2, 1983	**Notification to all candidates**

Applications may be obtained from:

The NIH Medical Staff Fellowship Program
Building 10, Room 2N220A
National Institutes of Health
Bethesda, MD 20205
Tel: 301-496-2427

Discrimination Prohibited: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the Medical Staff Fellowship Program must be operated in compliance with these laws and Executive Orders.

Foreword

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The National Institutes of Health and the Warren Grant Magnuson Clinical Center, the research hospital for the Institutes, are international centers for biomedical research and clinical investigation. The Clinical Center and the other intramural research facilities in Bethesda have provided research and training opportunities for thousands of foreign scientists and physicians and for an even greater number of research scientists and clinical investigators in this country.

The Clinical Center has 500 beds to which patients are admitted for participation in research protocols. The protocols are directed towards understanding disease as well as towards diagnosis and treatment. The proximity of the wards to the 1,200 research laboratories ensures continuing collaboration between clinical and laboratory scientists. Within this scientific community there are unique opportunities to acquire the skills necessary for biomedical research. This catalog describes the opportunities open to physicians and dentists in the Medical Staff Fellowship Program at the NIH.

Mortimer B. Lipsett, M.D.
Director
The Warren Grant Magnuson
Clinical Center

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art One

eneral Description of ledical Staff ellowships and ther Opportunities

he Warren Grant lagnuson linical Center

Mortimer B. Lipsett, M.D.,
Director
Jay R. Shapiro, M.D.,
Deputy Director

he Warren Grant Magnuson Clinical enter is a modern laboratory hospital acility shared by the 11 Institutes that onduct combined laboratory and clinical udy programs. This 500-bed research ospital is located on a 300-acre campus t the National Institutes of Health IH) in Bethesda, Maryland.

NIH is the largest biomedical research rganization in the world. Approximately ,500 staff members have doctoral egrees, including almost 1,000 with .D. degrees, more than 1,300 with h.D. degrees, and about 50 with .D.S. and 50 with D.V.M. degrees. A gnificant number have more than one octorate.

Three Nobel laureates work on the ampus: Drs. D. Carleton Gajdusek, ulius Axelrod, and Marshall W. irenberg. Dr. Gajdusek received the ward in 1976 for his work in proving hat kuru—a fatal disease affecting the ervous system—is a transmissible slow irus infection.

In 1970, Dr. Axelrod was cited for iscoveries concerning transmitter ubstances in nerve terminals and echanisms for their storage, release, nd deactivation. Dr. Nirenberg was onored in 1968 for his work on the ranslation of the genetic code and its unction in protein synthesis.

Three other scientists received the Nobel prize for work done while at NIH. In 1976, Dr. Baruch Blumberg was honored for his discovery of the "Australia antigen," a marker of hepatitis B. The prize was given to Dr. Anfinsen in 1972 for his studies of ribonuclease, particularly the relationship between amino acid sequences and the conformation of enzyme molecules. Dr. Arthur Kornberg received the award in 1959 for his research on the mechanisms in the biological synthesis of DNA and RNA.

With the help of a staff of almost 3,000 technical personnel, NIH scientists are involved in some 2,500 research projects which result in more than 5,000 published scientific articles each year. The budget for this intramural research effort is almost $413 million.

The 14-story Clinical Center represents an important resource for training in medical research. The hospital provides a setting in which a young physician can participate in medical care, acquire new clinical skills, and carry out research in a laboratory conveniently located a few steps from the patient's room. The center is designed to bring scientists working in laboratories into close proximity with clinicians caring for patients so that bench investigators and physi-

cians may collaborate on problem diseases.

The primary mission of the Clinical Center is to provide a specialized form of hospital care necessary for Institute studies. To accomplish this goal, the Clinical Center has developed patient care programs and related technical support systems which stand at the fore of modern health care.

The Nuclear Medicine Department provides whole-body scanning and diagnostic imaging through the use of radioactive pharmaceuticals. Positron emission tomography and radionuclide cineangiography are among the imaging techniques under study. The Diagnostic Radiology Department has a full complement of radiological equipment, including CAT scanners and ultrasonic scanners. Nuclear magnetic resonance and digital fluorographic devices are among those the department plans to acquire and evaluate. The superbly equipped clinical pathology laboratories provide optimum support to physicians and their patients. The Blood Bank provides blood products for the patients, teaches blood banking and immunohematology, and conducts research.

Numerous opportunities are available for medical staff fellows to participate in the use and development of modern medical computer systems, medical instrumentation and electronics. These systems are used for patient care, for clinical and basic research, and for the education of staff fellows in the use of computers in medicine.

A large, computer-based Medical Information and Communication System is used in support of patient care in the Clinical Center and the adjoining Ambulatory Care Research Facility. One hundred and fifty display terminals and 70 printers are located on the Clinical Center nursing units and in-service department areas to permit rapid retrieval of patient information and processing of medical orders. This system is used by physicians, nurses, and other medical professionals as part of their daily patient care activities. In addition, information obtained during the patien care process is available through the cen tral NIH computer facility for retrieval and research analysis.

The Clinical Center admits approximately 7,500 patients yearly. In addition the outpatient clinics service over 100,00 patient visits annually.

A newly completed 13-story Ambulatory Care Research Facility (ACRF), adjacent to the original Clinical Center structure, is designed to expand and strengthen the combined laboratory and patient care programs of the Clinical Center. It is estimated that the new win will double the Clinical Center's outpatient capacity. The facility will provid an optimum environment to care for an study outpatients, yet it will retain the same proximity between clinical and laboratory scientists that has successfully promoted medical inquiry in the existing Clinical Center.

The Clinical Center appoints medical staff fellows for the Departments of Clinical Pathology, Critical Care Medicine, Nuclear Medicine, and the Blood Bank. These programs are described in part three.

The Medical Staff Fellowship Program

Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists through appointments as medical staff fellows at the National Institutes of Health. These positions encompass most medical specialties and basic science disciplines.

Appointments to the Medical Staff Fellowship Program (formerly the Associate Training Program and encompassing what used to be designated clinical, research, and staff associate positions) are based on professional attainment, research interest, and ability. The NIH seeks outstanding candidates and selection is made without regard to race, sex, geographical location, or university affiliation. Candidates may be selected because of demonstrated excellence in research or in a clinical discipline. Selections are made through a matching process explained in part two.

Each medical staff fellow participates in a research program under the direction of a preceptor. Preceptors, drawn from a large number of skilled investigators, serve to enrich each staff fellow's experience. Because of the unique blending of clinical and nonclinical scientists, the staff fellow is in daily contact with scholars representing a variety of research interests.

The NIH offers many educational opportunities ranging from tutorials to sponsored lectureships. Postgraduate instruction, sponsored by the Clinical Center or the graduate program of the Foundation for Advanced Education in the Sciences, Inc., is available on a broad range of topics, including mathematics, languages, laboratory skills, and clinical reviews (see part four).

The NIH affords the medical staff fellow the opportunity to participate in clinical and laboratory research. Clinical activities are carried out near laboratory facilities and are under the immediate supervision of senior investigators. This proximity to patients and to collaborating scientists from many biological disciplines has created a superb environment for learning and performance of clinical research.

Some fellows devote most of their time to laboratory research in a biomedical science. The preceptor is responsible for training in research methods and design, and for guidance in the conduct of specific research undertakings and in the interpretation of results. One of the goals of the program is to select research problems which will enable the staff fellow to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The medical staff fellow position also provides opportunities for those highly qualified candidates who could contribute significantly to research areas not specifically designated in the research or clinical categories. In these cases, the staff fellow may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he or she works. Research experience may be supplemented by attending formal evening study courses, lectures by guest speakers and a variety of medical seminars.

The Dental Staff Fellow

Like medical staff fellows, the dental staff fellow may participate in laboratory and clinical research, and enhance professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the fellowship, there is full opportunity for a fellow to become familiar with all ongoing research programs relevant to dentistry; affiliate with one or more preceptors to participate in a mutually acceptable area of investigation; and extend scientific background through rounds, conferences, seminars, and formalized course work.

The Medical Staff Fellow in Pharmacology (Pharmacology Research Associate Program)
Staff fellows in this program, sponsored by the National Institute of General Medical Sciences, spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those committed to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

Staff Physicians
Some physicians, already qualified in a specialty, are not appointed as medical staff fellows but as staff physicians. Initial appointments are temporary and usually for 2 years, but some staff physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part-time in research.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to medical students. For 1982-83, the staffs of several Institutes are collaborating to supply an in-depth exposure to 13 clinical subspecialties: anesthesiology, clinical dental care, critical care medicine, computers in clinical medicine, endocrinology and metabolism, genetics, immunology, medical-surgical neurology, nuclear medicine, oncology-hematology, psychopharmacology, pediatric psychopharmacology, and surgical oncology. The National Institute of Dental Research offers a neurobiology elective for dental students.

The essence of this educational experience is close association between the student, staff fellows, and physician-scientists in several of the Institutes.

Students are assigned patients for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with interests in fields other than those listed above are sometimes arranged through communication between an NIH staff member and a faculty sponsor of the students.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Clinical Electives Program Office
Building 10, Room 2N220A
National Institutes of Health
Bethesda, MD 20205

Approved Training Programs

Residency training programs approved by the Accrediting Council on Graduate Medical Education are offered in anatomical pathology and nuclear medicine as are fellowships for advanced subspecialty training in blood banking and clinical pathology, including clinical chemistry, hematology, microbiology, and the laboratory computer service.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Jose Costa, M.D.
Chief, Laboratory of Pathology
Building 10, Room 1A25
National Institutes of Health
Bethesda, MD 20205

Eric Jones, M.D.
Acting Chief,
Nuclear Medicine Department
Building 10, Room 1B37B
National Institutes of Health
Bethesda, MD 20205

Board Certification: The first year of the clinical fellowship in the National Heart, Lung, and Blood Institute is accredited as a third year of training in internal medicine by the American Board of Internal Medicine. The 3-year medical Staff Fellowship has been accepted for training by the subspecialty board in Infectious Diseases and the conjoint Board of Allergy and Immunology.

Credit towards Board certification is offered in the following specialties and subspecialties:

- Allergy/infectious diseases
- Blood banking
- Cardiology
- Clinical chemistry
- Critical care medicine
- Dermatology
- Endocrinology
- Hematology
- Gastroenterology
- Genetics
- Internal medicine (NHLBI only)
- Medical oncology
- Microbiology
- Neurology
- Pediatric hematology/oncology
- Pediatrics
- Psychiatry
- Reproductive endocrinology (obstetrics and gynecology)
- Rheumatology

The amount of credit earned depends on the training completed and the acceptability of such to the individual Board. Candidates are advised to consult the appropriate Institute and specific subspecialty board for additional information.

Endocrinology Fellowship Program

The NIH Endocrinology Fellowship Program is an interinstitute program which involves most of the clinical branches working in this field on the campus at Bethesda. It is devised for physicians who seek a broad experience in both fundamental research and clinical experience in endocrinology. Fellows are selected for a period of 2 or 3 years which includes approximately 1 year of clinical activity among several endocrinology branches of the NIH. During this clinical period, fellows function as primary care physicians for the 70-bed endocrinology inpatient services, serve as consultants for other services of the 500-bed Clinical Center as well as for other local hospitals, and participate in outpatient work, rounds, and seminars. The remainder of the time is spent primarily in laboratory investigation under the direction of a senior investigator in one of the endocrinology branches. During this research period opportunity exists for continuing outpatient work and participation in clinical conferences. No position will be offered for a single year.

Medical staff fellows selected by any of the three endocrinology branches of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (Clinical Endocrinology, Diabetes, or Metabolic Diseases) as well as the Developmental Endocrinology or the Endocrinology and Reproduction Research Branch of the National Institute of Child Health and Human Development automatically participate in the interinstitute program. Medical staff fellows from other branches may participate only under special circumstances. The National Heart, Lung, and Blood Institute also participates in the interinstitute program.

Lectures and Courses
The NIH campus provides a stimulating intellectual environment for continuing

education, including multiple clinical and basic science conferences and journal clubs, as well as tutorial seminars and courses spanning many disciplines. The endocrinology fellowship program sponsors formal endocrinology seminars and lecture series covering the field broadly and in detail. The Computer Science Division and Radiation Safety Branch provide detailed practical work and study in these fields. The latter branch gives an intensive course in the use of radionuclides, enabling graduates to apply for their own radioisotope license after completion of the fellowship.

Medical Student Program

Students selected from various medical schools throughout the country participate in endocrinology courses offered three times yearly. Fellows work in close association with the students and supervise their patient care activities. These and other teaching functions help develop the fellows' skills as educators in preparation for later academic careers.

Internal Medicine and Endocrinology Board Examinations

Studies in the Clinical Center relate to all areas of internal medicine, and fellows are encouraged to develop their general clinical skills. Completion of the fellowship program satisfies requirements for the Endocrinology Subspecialty Board Examination. Because of recent changes in the requirements for the Certifying Examination of Internal Medicine, applicants are encouraged to review their residency training plans directly with the Board.

Prospective applicants who would like further information on the program should write Dr. Bruce D. Weintraub, Building 10, Room 8N315, National Institutes of Health, Bethesda, Maryland 20205.

Medical Genetics Fellowship Program

The NIH Interinstitute Medical Genetics Fellowship Program is a cooperative undertaking involving several clinical branches and research laboratories in six Institutes located on the Bethesda campus. It is a program of 2-, or in some cases, 3-year duration for physicians seeking broad exposure to both research and clinical experience in human genetics. The training is also designed to fulfill all requirements proposed by the American Board of Medical Genetics for fellowships leading to eligibility for Board certification.

The first year of the fellowship includes clinical activities and initiation of laboratory or clinical investigations under the direction of a senior scientist. Fellows will be responsible for patients seen at the weekly NIH Genetics Clinic and the NIH supervised Prenatal Diagnosis Clinic at George Washington University Hospital. They will also serve as genetics consultants in the 500-bed Clinical Center and will participate in conferences, rounds, and seminars. Further opportunity to become familiar with the spectrum of patients with genetic disease is provided by optional attendance at genetics clinics at collaborating institutions including the Children's Hospital-National Medical Center in Washington, D.C., and the Johns Hopkins Hospital in Baltimore.

The second year of the fellowship will primarily involve research activities initiated during the first year. Fellows may elect to pursue research chosen from many types of investigations related to genetic diseases; descriptions of the diverse interests of participating scientists are provided in a brochure which will be supplied to fellowship applicants. The NIH program aims to provide fellows with research experiences of the highest caliber and to prepare them for careers as independent investigators in human genetics.

The fellowship program includes a formal seminar series in medical genetics in which invited speakers discuss research and clinical topics of current interest, and other opportunities for continuing education (clinical and basic science con-

ences, journal clubs, tutorial seminars,
d postgraduate courses) are plentiful
the NIH campus. The fellowship pro-
m also sponsors a yearly 8-week elec-
e in medical genetics for senior
idents from medical schools around
country; fellows assist in didactic
ture-demonstrations on the approach
patients with genetic diseases and in
ervision of students in patient related
ivities. These and other teaching opportunities develop the fellows' skills as educators in preparation for future academic careers.

Applications for the fellowship program should be directed to the Medical Staff Fellowship Office (see p. 9). Further information may be obtained by telephone from Dr. Joseph D. Schulman at (301) 496-6683.

art Two

pplying for a edical Staff ellowship

bout 125 medical staff fellows are ap- ointed annually to positions emphasiz- g clinical or basic research. Fellows are nployed through the Public Health Ser- ice (PHS), but not in the Commissioned orps of the PHS.

Minimum eligibility requirements for ost medical staff fellowships is comple- on of 2 years of graduate medical train- g before entrance on duty. Application ould be made between 1 and 2 years efore desired date of appointment.

To be considered for a medical staff llowship, completed application forms ust be received in the NIH Medical taff Fellowship Office, Building 10, oom 2N220A, National Institutes of ealth, Bethesda, MD 20205, by ovember 22, 1982.

Participants in the National Health ervice Corps Scholarship Program are ot eligible for consideration until after ey have served obligated pay-back ears in NHSC-designated areas of edical need.

o be eligible for a PHS appointment as edical staff fellow, a candidate must eet the following requirements:

- Be a United States citizen or a permanent U.S. resident.
- Meet the medical fitness standards.
- Be a graduate of an accredited medical, osteopathic, or dental school.
- Satisfactorily complete an internship (PG1) approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)
- Have certification by the Educational Commission for Foreign Medical Graduates, or must have passed either the full examination of the National Board of Medical Examiners or the Visa Qualifying Exam.

Employment Benefits for Medical Staff Fellows

Medical staff fellows are entitled to the following benefits which are comparable to those offered to Civil Service employees: partial subsidy for health insurance and group life insurance, retirement benefits, occupational medical emergency service at NIH, compensation for injury, 13 working days of annual leave per year and the same amount of sick leave, and training at Government expense. Medical staff fellows will be paid for entry-on-duty travel to NIH and shipment of household goods. Return travel and shipping will also be paid to fellows who leave after completion of their initial assignment.

A repeat tour as a medical staff fellow is possible followed by appointment in the Commissioned Corps of the Public Health Service or appointments as an NIH senior staff fellow. Pay, allowances, and other benefits in the Commissioned Corps are comparable to those of officers of the Armed Forces.

Method of Selection—Matching Program

Selections for medical staff fellow appointments are made through a matching process in which the candidate's preferences are matched with the Institute's preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Checklist." After reading part three of this catalog, the candidate should check off on these sheets the areas in which he or she is interested. There is no limit to the number of interest areas which may be checked. The application will be sent to all laboratories and branches which the candidate has checked.

After thorough review by the Institutes of all applications, a limited number of candidates will be selected for persona interviews after which the candidate su mits his or her confidential preference list. *Applicants should only list progra in which they have an interest and wo accept if chosen. In a highly competiti selection system, failure to accept a po tion after the "match" compromises another candidate's opportunities.*

The NIH Medical Staff Fellowship fice will set up the interview and advis candidates when to report. Candidates are requested not to attempt to arrang their own interviews.

Part Three

Program Areas for Which Candidates May Apply

Each of the major NIH components has prepared a description of its program areas for which medical staff fellows may seek appointment. These descriptions are meant to anticipate many of the questions applicants may have in selecting program areas for which they wish to be considered. *It should be noted that a candidate is not limited as to the number of kinds of positions for which he or she may apply.*

National Cancer Institute

Vincent T. DeVita, Jr., M.D.,
Director, Clinical Director

Division of Cancer Biology and Diagnosis

—Alan S. Rabson, M.D., Director

The Division of Cancer Biology and Diagnosis is broadly concerned with biochemical, genetic, physiologic, immunologic, and metabolic derangements that predispose organisms to neoplasia and that result from neoplasia. Within this area, a wide variety of research interests are pursued which involve basic questions of immunology, virology, molecular biology, and biochemistry of normal and pathologic states.

The Division is composed of several branches and laboratories, each under the direction of a branch or laboratory chief. Medical staff fellow positions are available in many of these areas and fellows work exclusively with the branch or laboratory in which they are accepted. All fellows have a unique opportunity to become experienced scientists in their fields of interest and thereby initiate a career in academic medicine and research.

Appointments in Clinical Research

Clinical positions are available for medical staff fellows in the Metabolism Branch, Immunology Branch, Dermatology Branch, and the Laboratory of Pathology. Fellows participate in patient care directly related to the research interests of the branch and engage in general research under the direction of individual scientists. The scope and orientation of each of these positions depends, of course, on that of the particular branch or laboratory.

Appointments in Laboratory Research

Nonclinical positions are available in the Laboratory of Biochemistry, the Laboratory of Pathophysiology, the Laboratory of Molecular Biology, and the Laboratory of Immunobiology.

In general, fellows are engaged in original research under guidance of individual investigators who act as preceptors for the fellows.

Clinical Research Branches

Dermatology Branch—
Dr. Stephen I. Katz

The Dermatology Branch studies the growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic, neoplastic, and inflammatory states; protein synthesis by epithelium, especially of tonofilaments, keratohyalin, and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; physiology of lymphoreticular cells and lymphokine formation; and the biological activity of oncogenic viruses.

Also studied are experimental allergic contact dermatitis; scanning and transmission microscopy of normal and diseased skin and other tissues; scanning microscopy of the cell-surface structure in relation to the mitotic cycle and motility; genodermatoses; biochemical and ultrastructural aspects of melanogenesis in normal and melanoma tissue; biochemistry and keratinization; xeroderma pigmentosum, an inherited disease of sun sensitivity, and multiple cutaneous cancer with abnormal DNA repair; clinical, chemical, and ultrastructural effects of vitamin A on skin; the oncogenic potential of tumor viruses; the development of therapy of epithelial cancers, skin lymphomas, and keratinizing diseases of the skin.

Immunology Branch—
Dr. William D. Terry
Senior Investigators
Dr. Howard B. Dickler
Dr. Maryanna P. Henkart
Dr. Pierre A. Henkart
Dr. David M. Segal
Dr. J. Stephen Shaw
Dr. Gene M. Shearer
Dr. Alfred Singer
Dr. Dinah S. Singer
Dr. John R. Wunderlich

- Immunotherapy Section—
  Dr. Richard J. Hodes
- Transplantation Biology Section—
  Dr. David H. Sachs

The Immunology Branch is concerned with the chemistry, genetics, biology, and clinical significance of immunity. Cellular immunity, transplantation immunity, and the nature of mammalian cell surfaces are the fundamental areas developed within the branch. Information derived from each of these areas is applied to studies of the relationship between the immune system and neoplastic cells in experimental animals and man.

Biochemical, biophysical, genetic, morphologic, biological, and clinical investigative techniques are utilized in these studies.

Cellular Immunity—The cell-mediated immune responses of laboratory animals and human beings are being investigated. The responses studied *in vitro* include cellular proliferation, cell-mediated cytotoxicity, and antibody production. Immune mechanisms which could be relevant for autologous neoplastic cell rejection are investigated. Immunity to chemically modified autologous cell-surface antigens, to autologous cells infected with influenza virus, immunity of F_1 hybrid cells to parental antigens, and cellular immune responses to cultured/syngeneic tumor cell lines represent the models under study. The role played by the major histocompatibility complex (MHC) both with respect to the MHC-product-associated immunogenic complexes found and to MHC as well as non-MHC immune response genes controlling reactivity to these immunogenic complexes is under investigation.

The nature of regulatory influences on the cell-mediated immune response to transplantation antigens is being investigated. Both synergizing and suppressive lymphoid subpopulations have been characterized in *in vitro* systems. Further work is being directed at the mechanisms of such regulatory influences, the role and expression of products of the *I* region of the MHC in these events, and the potential relevance to *in vivo* phenomena including transplantation and tumor immunity.

The mechanisms by which immune, as well as nonimmune lymphoid cells kill specific target cells are also under investigation. *In vitro* studies are utilized to evaluate direct killing of mammalian cells by "killer" lymphocytes, and attempts are made to relate findings to *in vivo* functions of cytotoxic lymphoid cell populations. Studies characterizing the nature of antibody-mediated, lymphocyte-dependent target cell killing are in progress.

The receptors for immune complexes (Fc receptors) on different immunocompetent cell populations are being characterized by a variety of methods. The interactions of these receptors to antigens determined by the immune response gene region of the MHC (Ia antigens), surface IgM and IgD, as well as to other cell-surface molecules are being investigated. The role of this receptor and these interactions in the immune response and the regulatory role of antibody are currently being studied.

Humoral Immunity—A number of *in vitro* assays have been developed and characterized in the mouse including: (a) primary and secondary antibody plaque-forming cell assays, T-cell proliferation assays, and antibody-secretion-enzyme linked immunoassay for use with a variety of antigens, including those under genetic control; and (b) T-lymphocyte and accessory cell independent B-cell responses to antibodies specific for antigen receptors plus T-cell replacing factor(s). These assays are being used (1) to evaluate the cellular level of expression of immune response genes and the mode of action of such genes, (2) to evaluate the role of cell-surface antigens determined by the *I* region of the H-2 complex and the role of subpopulations of cells bearing these antigens, (3) to characterize the nature and mechanism of action of antigen-specific helper and suppressor factors, and (4) to evaluate the immunologic role of idiotype-bearing molecules of both T- and B-lymphocyte origin, and (5) to use purified factors and monoclonal antibodies to characterize the cell-surface molecules responsible for triggering and/or regulation of responses. Antibodies to idiotypic specificities of antibodies, the levels of which are regulated by immune-response genes, are being used as probes in these studies.

Transplantation Immunity—Antibodies against histocompatibility antigens and tumor antigens are used as reagents for determining the nature of these antigens and manipulating the immune response against them. Studies utilize inbred rats and mice and congenic mice. Strains of miniature swine are also being developed to provide large quantities of materials for chemical characterization of surface antigens and as a model for organ transplantation studies.

Antibodies with specificities directed against transplantation antigens are being examined for chemical and immunologic individuality. Mouse lymphocyte alloantigens determined by genes in the *Ir* region (Ia antigens) are being studied serologically and functionally. Hybridomas producing monoclonal anti-H-2 and anti-Ia antibodies are being produced and characterized. Receptors of these antibodies are being examined for unique and for shared idiotypes.

Human allogeneic T-cell responses are being used as a probe to define new antigens in the HLA regions. New gene products already defined by this approach are being studied for their relevance in regulating human immune responses and for association with human diseases.

Cell Membranes—The chemistry of lymphoid cell membranes is being investigated in an effort to characterize the molecular makeup of surface components as well as to identify and study specific functional receptors. Simple defined membrane systems are being designed to model immunologic phenomena such as cell-mediated cytotoxicity and patching and capping of surface antigens. The nature of the membrane lesion generated by different types of cell-mediated killing (T-cells, K-cells, etc.) is under investigation.

Immunochemistry—The structural and biological consequences of antigen-antibody interactions are being examined by using affinity cross-linked oligomers of IgG antibodies as models for naturally occurring immune complexes. The oligomers are being used to characterize immunoglobulin receptors on various cell types, to assess the effects of antibody polyvalency on cell binding, and to study the physiological consequences of the interactions of cross-linked immunoglobulins with cells. Affinity cross-linked oligomers are also being used to study the interaction of complement with IgG antibodies.

Tumor Immunology—Cellular immune mechanisms of tumor-bearing animals and patients with a variety of malignancies are studied, and attempts are made to modify reactions so as to improve tumor cell kill. Specific assays are established to determine the presence of humoral and cell-mediated responses of hosts to tumors.

Alternative assays are being tested for use in detecting early events in the recognition of malignant cells by host immune lymphoid cells. By means of such assays, attempts will be made to define at a structural level the characteristics of tumor cell-surface antigens which render these cells either susceptible or resistant to immune destruction in the tumor-bearing hosts.

Immunotherapy of tumors is approached both in animal models and patients using nonspecific and specific stimulation of the immune system. A clinical study is now in progress to evaluate the effectiveness of adjuvant therapy in preventing recurrence of malignant melanoma in patients who have been rendered clinically free of disease but who have poor prognosis in the absence of therapy. Comparison is being made between adjuvant chemotherapy with methyl-CCNU and immunotherapy with either BCG alone or BCG plus a vaccine of neuraminidase-treated allogeneic melanoma cells. In addition to monitoring the clinical status of these patients, laboratory tests are carried out to study the immune responses induced by the therapy.

Molecular Immunology—Investigation of the molecular mechanisms that regulate the expression and synthesis of histocompatibility antigens has been recently initiated. A genomic DNA segment containing a functional MHC gene has been isolated. The regulation of expression at the MHC gene in a heterologous cell and the DNA sequence organization of the entire genomic segment are currently under investigation.

Metabolism Branch—
Dr. Thomas A. Waldmann

- Immunophysiology Section—
  Dr. Warren Strober
- Cellular Immunology Section—
  Dr. R. Michael Blaese
- Endocrine Section—
  Dr. James M. Phang

The Metabolism Branch is broadly concerned with clinical and laboratory studies that focus on the immunologic, endocrinologic, and metabolic bases of disease occurring in patients with neoplasia.

Immunologic interests encompass studies of immune regulation, including factors controlling helper and suppressor T-cell function in immunodeficiency states (hypogammaglobulinemia, IgA deficiency, Wiskott-Aldrich syndrome, and ataxia telangiectasia), in leukemias of T-cells, as well as in animal models of disordered immunity. Other areas of immunologic interest include studies using recombinant DNA technology to examine the genes controlling immunoglobulin synthesis and their organization and studies of the genetic basis of immunity, including the relationship between HLA antigens and disease (gluten-sensitive enteropathy) and genetic factors controlling the response to complex chemically defined proteins; studies of cytotoxic effector mechanisms and the role of macrophages in the afferent and efferent limb of the immune response; studies of gastrointestinal (GI) tract immunology, including the investigations of intestinal lymphangiectasia GI allergy, inflammatory bowel disease, and GI abnormalities associated with immunodeficiency; studies of patients with lymphoproliferative neoplasms including multiple myeloma and chronic lymphocytic leukemia; and T-cell leukemias including Sezary syndrome, with the aim of defining the T-cells with retained immunologic functions. The isolation and characterization of immunoregulatory biological modifiers is being performed using cloned T-cell lines and T-T cell hybridoma technology.

Endocrine interests include biochemical studies of amino acid metabolism related to collagen synthesis and gluconeogenesis (studies of regulation of enzymes in the collagen synthetic pathway and the proline degradative pathway). These are related to studies of patients with disorders of metabolic bone disease, diabetes mellitus, and aminoacidopathies. Studies of growth hormone, somatomedin, and other growth peptides are related to studies of patients with growth disorders.

Basic Research Laboratories

Laboratory of Biochemistry—
Dr. Maxine Singer

The emphasis of the work in the laboratory is on the relation between structure and function in biological systems and on the regulation of cellular processes. The research involves prokaryotes and a range of eukaryote systems selected because of their potential for yielding important information on cellular structure, function, regulation, development, and differentiation. The study of regulation encompasses regulation of gene expression, regulation by interaction of macromolecules, and regulation of cells by hormones and ions. Work is carried out on both the molecular and cellular level. Techniques include those of biochemistry, physical chemistry, cell biology, and molecular genetics.

- Biochemistry of Gene Expression Section—
  Dr. E. Brad Thompson

Control of gene expression in eukaryotic cells and its application to clinical medicine are studied. The effects of steroid hormones on enzyme induction in cultured cells and cell hybrids are investigated, along with studies on steroid receptors in human leukemia and breast cancer. The molecular details of steroid action are rapidly being learned, providing an excellent model for studying the general question of gene expression in animal cells. In this section, a combination of cell genetic—variant cell lines, hybrids—and biochemical techniques—mRNA translation, RNA and DNA analysis, DNA cloning—are being used. Clinical applications are made when feasible.

- Biosynthesis Section—
  Dr. Edward L. Kuff

Studies on molecular and functional properties of tumor virus nucleic acids, the enzymatic mechanism of DNA synthesis, and the regulation of collagen biosynthesis and secretion in normal and transformed cells are the concern of this section. Technical approaches include analysis of nucleic acid sequence relationships and genomic organization, isolation of subcellular and viral components, purification of DNA polymerases and their use in constructing *in vitro* synthetic systems, and the characterization of enzymes and cofactors involved in sequential processing of newly formed collagen.

- Cellular Regulation Section—
  Dr. Martin Rosenberg

Studies concern the mechanisms of regulation of gene expression at the molecular level in both prokaryotic and eukaryotic organisms. In particular, the section studies the precise nature of various protein-nucleic acid interactions that are used to control gene expression at the levels of both transcription and translation. A variety of regulatory signals, which control the initiation, termination, and post-transcriptional processing of RNA in bacterial, viral, and higher cellular systems are being studied. Recombinant DNA technology is used to introduce and examine the expression of "foreign" genes into heterologous cell systems and construct hybrid cloning vehicles that allow overproduction of a variety of specific gene products in bacterial cells. Techniques of molecular biology are also used to study genome organization.

- Developmental Biochemistry Section—
  Dr. Igor B. Dawid

Studies on the biochemical processes in development and differentiation are investigated with particular emphasis on regulatory phenomena. The structure of selected components of the genome of several animal species is studied, as well as gene expression during the development of germ cells and embryos. Currently under study are certain nuclear genes active in early frog embryos, the ribosomal genes, a class of transposable elements, and the functional organization of chromatin in *Drosophila;* and genes encoding muscle-specific proteins in chickens.

- Macromolecular Interactions—
  Dr. Claude B. Klee

Studies are directed toward the understanding of the mechanism of coupled regulation of cellular processes by Ca^{2+}, calmodulin, and cyclic nucleotides. Enzymes regulated by calmodulin are characterized and then interaction with calmodulin and other regulatory ligands are studied at the molecular level as well as in eukaryotic cells in tissue culture.

- Nucleic Acid Enzymology Section—
  Dr. Maxine Singer

Studies pertain to a variety of nucleic acid structural and functional relationships in cellular and viral eukaryotes. Of particular interest is the organization of primate DNA, and the origin, structure, and biology of simian virus 40 and its DNA.

- Protein Chemistry Section—
  Dr. Elbert A. Peterson

Studies are in progress on the biochemical changes accompanying differentiation and maturation of leukocytes and the nature of hormonal factors controlling these processes; the biological transfer of genetic information via isolated chromosomes or DNA and its application to genetic mapping; the interactions between cells involved in the immune response and the identification and isolation of participating cell types; and the development of new physical and immunological methods for the purification of cell populations, subcellular organelles, and proteins.

Laboratory of Cell Biology—
Dr. L. W. Law

Personnel of this laboratory have diverse interests focusing on the study of transformation of a normal cell to a neoplastic cell. Some of the specific problems pursued are: genetic control of the synthesis of abnormal proteins produced by malignant cells, principally plasma cells; role of cell membranes in regulating differentiation and growth; identification and study of tumor antigens and of the specific immune reactions initiated; solubilization and purification of transplantation and tumor antigens; influence of somatic cell hybridization on expression of genetically determined events; and ultrastructural analysis and molecular biology of viral oncogenesis. Techniques from virology, immunology, immunochemistry, biochemistry, biophysics, tissue culture, somatic-cell hybridization, and electron microscopy are used in these studies.

- Office of the Chief

Investigations are conducted in collaboration with the chemistry unit on the biologic, biochemical, and chemical characteristics of solubilized and purified H-2, HL-A, and tumor antigens on the cell membrane. Studies are also in progress on the immune response of the tumor-bearing animal and response to solubilized tumor antigens.

- Somatic Genetics Unit—
  Dr. H.C. Coon

This unit is studying the genetics and transforming capacity of mitochondrial DNA and the characteristics of somatic cell hybrids, particularly those employing neuron hybrids.

- Chemistry Section—Dr. E. Appella

Biochemical, biophysical, and chemical studies are conducted on solubilizing and purifying tumor antigens and histocompatibility antigens (H-2, HL-A). The unit is also investigating the epoxide hydrase mechanism in the metabolism of chemical carcinogens, the chemistry of Edman degradation, and new supports for solid phase degradation.

- Cell-Mediated Immunity Studies Unit—
  Dr. C. C. Ting

This unit studies mechanisms of tumor cell killing in syngeneic systems using several cell-mediated assays; also the role of humoral factors, suppressor cells, and helper cells.

- Immunochemistry Section—
  Dr. M. Potter

This section focuses on the chemistry of immunoglobulins secreted by plasma cell tumors, the factors concerned with initiation and growth of myelomas, and the antibody combining sites of myeloma proteins.

- Ultrastructural Biology Section—
  Dr. N. A. Wivel

Laboratory investigations focus on factors that contribute to cell differentiation and malignant transformation with particular emphasis on systems where oncogenic viruses represent the carcinogenic agent.

- Viral Oncogenesis Section—
  Dr. Kenneth S. S. Chang

In vitro and *in vivo* systems are used to study the interaction between oncogenic viruses, principally RNA-contained and host cells with special attention directed to host specificity; the genetic factors influencing susceptibility; the role of endogenous viruses in the etiology of reticulum cell sarcomas; and the characterization of features that distinguish viral structural antigens from tumor-associated antigens in the leukemias.

Laboratory of Immunobiology—
Dr. Tibor Borsos

- Section on Cellular Immunity—
  Dr. Berton Zbar

Cell-mediated immunologic reactions are studied for their capacity to inhibit the growth and spread of experimental cancers. Mycobacterial adjuvants and murine retroviruses are used to augment host response to tumor cells. A variety of animal and *in vitro* models are being used in attempts to delineate the mechanisms of these reactions.

- Section on Humoral Immunity—
  Dr. Tibor Borsos

Antibody- and complement-mediated cytotoxic reactions are studied for the mechanism of action. The primary goal is to understand the molecular basis of complement action and the molecular basis of cell defense mechanism against complement attack. Purification of antibodies, complement components, cell membrane receptors, and studies of synthetic pathways that control cell membrane integrity are also part of the study.

- Section on Immunopathology—
  Dr. Edward J. Leonard

Alterations in cellular immune function in pathological conditions are studied. Projects include mechanisms of macrophage activation, serum factors that alter macrophage function, the nature of depressed mononuclear phagocyte chemotaxis in patients and animals with neoplasms, the mechanisms of basophil accumulation in delayed hypersensitivity reactions, and the production and chemical nature of lymphotoxin.

Laboratory of Molecular Biology—
Dr. Ira Pastan

- Biochemical Genetics Section—
  Dr. Max Gottesman
- Gene Regulation Section—
  Dr. Benoit de Crombrugghe
- Cell Organization Section—
  Dr. Seymour Wollman
- Ultrastructural Cytochemistry Section—
  Dr. Mark Willingham

- Membrane Biochemistry Section—Dr. Kenneth Yamada
- Developmental Genetics Section—Dr. Sankar Adhya
- Molecular Cell Genetics Section—Dr. Michael Gottesman

A major focus is on how genes function to control cell behavior. Attention is devoted to the genetic and biochemical alterations that occur when normal cells are transformed to cancer cells by tumor viruses and to alterations in cyclic AMP, cell-surface protein, and collagen synthesis. The tools of somatic cell genetics, including mutant isolation, karyotyping and chromosome transfer, are extensively employed. Certain genes, such as the *src* gene of Rous sarcoma virus, and collagen, whose synthesis is altered by the *src* gene in malignant transformation, are cloned in *Escherichia coli* by recombinant DNA techniques to permit analysis of their altered expression in cancer cells. Studies are carried out on cellular ultrastructural organization that enables cells to move and carry out receptor-mediated endocytosis, phagocytosis, pinocytosis, and mitosis. The laboratory conducts a research program that involves the identification, cloning, and characterization of genetic elements involved in the control of transcription initiation and termination in cells; it also studies the regulation of regulatory proteins themselves, e.g., adenylate cyclase and cyclic AMP receptor protein. Other research is carried out on the mechanism of excision and integration of viral genomes and the initial steps in the replication of the DNA of some DNA coliphages.

Laboratory of Pathology—
Dr. Alan S. Rabson

- Surgical Pathology and Postmortem Section—Dr. Jose Costa
- Hematopathology Section—Dr. Elaine S. Jaffe
- Cytopathology Section—Dr. Elizabeth W. Chu
- Comparative Oncology Section—Dr. Clyde J. Dawe
- Biochemical Pathology Section—Dr. David A. Zopf
- Ultrastructural Pathology Section—Dr. Timothy J. Triche
- Viral Oncology and Molecular Pathology Section—Dr. Peter M. Howley
- Image Processing Section—Dr. Lewis E. Lipkin
- Pathological Technology Section—Barbara Coolidge

The Laboratory of Pathology of the National Cancer Institute offers a 2- to 3-year training program for residents in pathologic anatomy. This program, which is fully approved for Board certification, provides well-supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology, and neuropathology can be arranged. The research activities of the staff are varied, and participation in clinical or basic research projects is an intrinsic part of the program during elective periods. Research interests of the laboratory include: viral oncology, molecular biology, immunopathology, immunochemistry, mechanisms of metastasis, comparative oncology, and tumor biology.

In addition, the laboratory offers research training in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies of viruses and neoplastic cells.

Laboratory of Pathophysiology—
Dr. Pietro M. Gullino

A group of projects concerning the mammary gland is carried on in connection with the Office of the Chief. Dr. Knazek studies the mechanism of prolactin action and role of prostaglandins on hormone receptor development. Dr. Vonderhaar evaluates the role of thyroid hormone-prolactin interactions on mammary gland development and tumorigenesis. Dr. Qasba, using recombinant DNA technology, is studying the expression of differentiated functions during growth and regression of normal and neoplastic mammary glands. Dr. Liotta studies the mechanism of tumor invasion and metastases, the synthesis and turnover of connective tissue components by normal mammary epithelium and by human mammary carcinomas, and Dr. Gullino works on the mechanism and prognostic value of angiogenesis in neoplastic and preneoplastic tissues.

- Section on Cellular and Molecular Physiology—Dr. Herbert L. Cooper

This section studies the biochemical mechanisms that control early stages of cell growth induction in normal and neoplastic human cells. Emphasis is on the mechanisms which maintain physiologically resting cells in the nongrowing condition and the early biochemical modifications that occur on growth stimulation. Current studies examine translational controls and post-translational protein modifications in human lymphocytes and the specific protein synthetic responses to growth regulatory agents, such as interferon.

- Section on Cell Cycle Regulation—Dr. William Kidwell

Laboratory investigations are concerned with characterization of biologic events uniquely required for the cell to progress through S, G_2, M, G, and G_0 phases. Emphasis is placed on the nutritional, hormonal and other factors involved in initiation of cellular transition through division to a differentiated state and the interrelationship among various organ cell types in this progressive change. Specific studies relate to the interaction of epithelial, myoepithelial, stromal cells, and adipocytes in the proliferative response of the mammary gland to hormones.

- Section on Cellular Biochemistry—Dr. Yoon Sang Cho-Chung

This section studies the mechanisms controlling cell growth and regression. Emphasis is placed on the roles of cyclic nucleotides, hormones, and other intracellular mediators in the growth control of normal and neoplastic cells. Current studies involve the mechanism of action of cyclic nucleotides in the regression of mammary tumors and suppression of mammary carcinogenesis.

- Section on Membrane Biology—Dr. Pedro Pinto da Silva

This section investigates the structure and dynamics of biological membranes, using freeze-fracture and freeze-etch electron microscopy alone or in combination with cytochemical labeling techniques.

- Section on Radiation Biology—Dr. Peter Riesz

The section is involved in the use of radiation to destroy bone marrow in order to study the laws governing marrow transplantation from donors. The effects of ionizing and UV radiation on nucleic acids and proteins are also being studied. The role of free radicals in biology is being investigated by electron spin resonance and spin-trapping.

Laboratory of Theoretical Biology—
Dr. Mones Berman

The laboratory is concerned with the formulation of theories of structure, function, and dynamics of biological systems, with the development of models for these systems, and with the development of mathematical and computational techniques for modeling and data analysis. Several areas are of particular interest: kinetics of metabolic systems and therapeutic agents; membrane structure and function, including transport through artificial lipid bilayer membranes, interaction of lipid vesicles with cells, dynamics of cell surface components, and assembly of proteins into membranes; receptors and hormonal regulation; immune response systems and carcinogenesis; configurations and properties of proteins, polypeptides, and other macromolecules. Although the work is predominantly theoretical, experimental studies related to these problems are carried out within the laboratory and in collaboration with others.

Division of Cancer Cause and Prevention

—Dr. Richard H. Adamson

The Division of Cancer Cause and Prevention plans and directs a national program of laboratory, field, and demographic research on the cause and natural history of cancer and means for preventing cancer through direct intramural research, research grants, and contracts; evaluates mechanisms of cancer induction and promotion by chemicals, viruses, and environmental agents; serves as the focal point for the Federal Government on the synthesis of clinical, epidemiologic, and experimental data relating to cancer; and participates in the evaluation of and advises the Institute Director on program-related aspects of the other grant and cancer control activities as they relate to cancer cause and prevention.

Carcinogenesis Intramural Program— The Carcinogenesis Intramural Program conducts a basic laboratory research program on the causes of cancer by chemical, physical, and biological (viral) factors; and on the pathogenesis and prevention of various cancer.

Field Studies and Statistics Program— Dr. Joseph F. Fraumeni, Jr., Associate Director

Environmental Epidemiology Branch— Dr. Joseph F. Fraumeni, Jr.

The Environmental Epidemiology Branch, in the Division of Cancer Cause and Prevention, combines a program of clinical oncology with etiologic research. Medical staff fellows appointed for 3 years spend their first year as primary-care physicians while their remaining 2 years are on the Clinical Oncology Program oncology service which is devoted to epidemiologic and etiologic research. Studies are undertaken to clarify the risk of cancer among persons exposed to occupational, iatrogenic, or other environmental hazards and among persons with genetic or immunologic predisposition. Physicians selected for this program need not have specific training in epidemiology or genetics, but should be alert to etiologic clues derived from clinical observations. In studies of high-risk groups, including cancer-prone families, the fellows are encouraged to collaborate with laboratory investigators in an effort to elucidate mechanisms of cancer susceptibility.

Medical staff fellows may participate in a wide variety of epidemiologic investigations in the branch and gain experience in the techniques of epidemiology. Weekly seminars are held to discuss ongoing projects.

Also available in the branch are 2-year medical staff fellow positions, which do not include the first year of patient care experience.

Division of Cancer Treatment

—Bruce A. Chabner, M.D., Acting Director

This Division carries out a broad program of basic and clinical research concerning the treatment of cancer. The major areas of research are radiation therapy, drug therapy, modifiers of tumor growth and differentiation, and surgical approaches to cancer treatment. Treatment programs are multidisciplinary in nature, involving the cooperative efforts of medical, surgical, and radiotherapy staff members.

Cancer Therapy Evaluation Program—
Dr. Daniel Kisner, Acting Associate Director

One medical staff fellow position is open each year within the Cancer Therapy Evaluation Program. The fellow is assigned to the Investigational Drug Branch for 1 year. Subsequently, a second year program may be developed in conjunction with other branches or laboratories within the Division of Cancer Treatment, or within the Cancer Therapy Evaluation Program by rotating to the Clinical Investigations Branch. It is anticipated that the second-year medical staff fellow will also maintain some responsibility for drug monitoring. Eligibility for a third year within the program is feasible. The duties within the Investigational Drug Branch include developing and coordinating clinical research efforts on specific new antineoplastic drugs developed by the NCI. Special projects in the area of antineoplastic drugs are available. The work within the Clinical Investigations Branch includes monitoring research and progress in grant and contract programs, reviewing new research protocols, developing new research strategies along disease or modality lines, providing overviews of research topics, and planning discussion groups and intergroup studies.

The major function of the Cancer Therapy Evaluation Program is to sponsor clinical trials of investigational and known antineoplastic treatment modalities and to monitor those trials. The scope of the program has evolved from broad drug trials with investigational chemotherapeutic agents to a disease-oriented approach. This includes the incorporation of effective chemotherapeutic combinations in early stages of disease and testing of new modalities, such as immunotherapy in combination with surgery, radiotherapy, and chemotherapy in specific disease entities until now considered untreatable. For these purposes, the program has planned and helped organize several study groups as part of a Clinical Contract Program designed to test combined modality approaches to specific diseases. The program also supports, through the grant mechanism, various clinical cooperative groups made up of institutions of higher education. These cooperative groups share in the design, development, execution, and analysis of clinical protocols. The program encourages and sponsors disease-oriented meetings with representatives from all interested groups to achieve coordination of clinical research efforts at a national level. Staff members of the program periodically attend meetings of the clinical contract and cooperative groups, disease-oriented task forces, and working parties. In addition, the program serves as a vehicle of communication between in-house preclinical and clinical programs and extramural activities.

The program coordinates clinical conferences sponsored by the chemotherapy area, which is an important mechanism for informing clinical investigators throughout the world on the status of drug trials. The conferences are held to discuss the clinical programs concerned with drug development. The program also maintains a special relationship with the Clinical Oncology Program's branches and the Baltimore Cancer Research Center. In addition, it is responsible for the development of new areas of clinical research and dissemination of information on clinical trials to investigators in foreign countries, and is responsible for receiving and analyzing information from abroad.

Clinical Investigations Branch—
Dr. William DeWys

The Clinical Investigations Branch monitors and coordinates a broad range of research activities. This includes research support for individual investigator-initiated projects (R01), program project grants (P01), cooperative group grants (R10), planning grants (P20), and research contracts. This research spans the spectrum from laboratory research to phase III clinical trials. Staff responsibilities include critical review of protocols developed by grant-supported cooperative groups and participation in the development of protocols for contract groups and intergroup studies. Staff members also develop overviews of research progress, formulate strategies for future research directions, and plan discussion groups on selected topics. There is a major emphasis on integration of modalities in the treatment of cancer.

This branch also maintains liaison with international clinical research groups and the Breast Cancer Task Force and Organ Site Programs of the National Cancer Institute.

- Medicine Section—
  Dr. John Y. Killen, Jr., Acting

This section reviews, monitors, and coordinates studies related to medical oncology and hematology, including studies of supportive care, basic investigations, and clinical trials. Members evaluate and stimulate research in chemotherapy (Phase II and III) and in the design of comprehensive therapeutic programs aimed at improving response to therapy and increasing the cure rate for specific neoplastic diseases.

- Nutrition Section—
  Dr. William D. DeWys

This section plans, develops, evaluates, and administers grant- and contract-supported research concerning the role of nutrition in the care and treatment of cancer patients. Areas of interest include the mechanisms of nutritional derangement in cancer patients, the prognostic effect of altered nutritional status, the application of basic nutritional research to the cancer patient, and the development of innovative approaches to the nutritional management of cancer patients.

- Pediatric Section—
  Dr. Richard Ungerleider

This section is responsible for review, evaluation, and stimulation of multimodal approaches to the treatment of childhood malignancies. This includes development and monitoring of phase I-II clinical trials in pediatric malignancies, liaison with investigators at cancer centers treating childhood malignancy, and monitoring and interacting with investigators in the Clinical Cooperative Groups involved in pediatric cancer.

- Surgery Section—
  Dr. Bimal Ghosh

This section plans, evaluates, and administers grant- and contract-supported research concerning the role of surgery in the care and treatment of cancer patients. Topic areas of interest include evaluation of new or modified surgical techniques; development of techniques for vascular infusion, perfusion, and occlusion; tumor immunology; biology of metastases; staging procedures; and evaluation of prognostic factors in the surgical treatment of cancer patients.

Investigational Drug Branch—
Dr. Daniel Hoth, Acting

This branch monitors and coordinates the drug-oriented trials of the Division. The branch serves as a link between the preclinical and clinical aspects of the drug development part of the Division with special interest in the pharmacologic investigations of new drugs. Interaction with investigators is a vital part of the work of the branch in providing supervision, advice, and retrieving information on therapeutic response and toxicity.

- Regulatory Affairs Section—
  Dr. John S. Penta

The section provides liaison with the Food and Drug Administration and supervises the preparation of all FDA filings on new drugs. This involves a close working relationship with intramural branches and committees dealing with submission of data to meet regulatory requirements.

- Drug Evaluation and Reporting
  Section—Dr. Silvia Marsoni, Acting

The section reviews, coordinates, and monitors protocol studies for phase I and early phase II clinical trials supported under contract. The section prepares annual reports on IND drug studies and investigates and reports on Adverse Drug

Reactions for all IND's. It is also responsible for the supervision of drug distribution, whether initiated by cooperative or contract groups or by Cancer Research Centers.

Radiotherapy Development Branch—
Dr. David Pistenma

The Radiotherapy Development Branch (RDB) of the Division of Cancer Treatment was created in the NCI reorganization of 1978. Its antecedent was the Radiation Program of the Division of Cancer Research Resources and Centers which emerged as an identifiable entity in the mid-1960's. In 1972, with the increasing workload, a second program director was added, a program director for radiation biology and physics to complement a rotating program director for radiation therapy. In the years since, the program maintained a steady rate of growth and its three major areas of concentration emerged: high-LET (linear energy transfer) radiotherapy, hyperthermia, and drugs that modify tissue response to radiation.

The RDB is responsible for administering a recently funded $1 million contract-supported program (over 10 years) in clinical fast neutron radiation and also has component parts including a traditional grant program (R01) of $17.7 million and a program project (P01) grant program of $21.4 million. The RDB staff also is responsible for the administration of contract-supported clinical research in brain tumors through the Brain Tumor Study Group and radiotherapy clinical research through the Radiation Therapy Oncology Group. The RDB staff includes Dr. David Pistenma, chief, and Drs. Frank Mahoney, Thomas Strike, and Barrie Jones.

Clinical Oncology Program—
Dr. Samuel Broder,
Acting Associate Director

The Clinical Oncology Program (COP) recruits approximately 18 medical staff fellows each year for a 3-year assignment in medical oncology or a 2-year assignment in surgical oncology. Fellows are recruited for one of the following clinical branches: Medicine, Pediatric Oncology, Radiation Oncology, and Surgery, located in the NIH Clinical Center on the Bethesda campus, or NCI-Navy Medical Oncology Branch located at the National Naval Medical Center, Bethesda, Maryland.

The 3-year medical oncology training program is offered to candidates who have at least 2 years of postgraduate training (internship and first-year residency) in medicine or pediatrics. The first year consists of primary responsibility for the clinical care of both inpatients and outpatients. The staff fellow may sometimes take a full year with a single clinical service, or elect two 6-month rotations through the clinical services of the COP. The second and third years consist of clinical and/or laboratory research under the supervision of a member of the senior staff. Associates will have opportunity to select a project from the numerous current studies in the laboratories of the Clinical Oncology Program and the Developmental Therapeutics Program. Opportunities are also available for clinical trial monitoring in the Cancer Therapy Evaluation Program. Clinical electives are available on consultative services in the branches and other related departments, and in various procedures, such as peritoneoscopy. Second- and third-year medical staff fellows continue to follow patients in the Outpatient Department. Offered throughout the program are lectures, clinical conferences, research seminars, teaching rounds, and joint conferences relevant to the field of clinical oncology and cancer research.

Candidates otherwise qualified who successfully complete the program are eligible for Board certification in the subspecialty of medical oncology or pediatric hematology-oncology.

For further information, applicants to the medical or pediatric oncology training programs should write to:

Associate Director
Clinical Oncology Program
National Cancer Institute,
Building 10, Room 6B15
Bethesda, MD 20205.

The Surgery Branch offers a 2-year surgical oncology training program. This program consists of a 6-month period on the wards of the Surgery Branch, inpatient and outpatient services, and 1½ years in one of the laboratories of the senior staff in the Surgery Branch. Selected medical staff fellows may remain for a third year to continue their laboratory research. Applicants interested in the Surgery Branch program should write director Dr. Steven Rosenberg.

Clinical Pharmacology Branch—
Dr. Charles Myers

This group conducts laboratory and clinical research activities on problems of drug action and toxicity in man and, as such, plays a supporting role for the chemotherapy programs of the other clinical branches of the NCI. The branch does not have patient care responsibilities of its own, but accomplishes its clinical studies through collaborative ties with the other clinical branches. Research training opportunities are available for physicians completing 1 year of clinical training in the Clinical Oncology Program or for trainees of the Clinical Pharmacology Training Program of the National Institute of General Medical Sciences.

Areas of specific research interest include: mechanisms of adriamycin cytotoxicity; mechanism of action and cellular pharmacology of antimetabolites; pharmacokinetics and metabolism of established and new antineoplastic agents; clinical and experimental applications of cytofluorometry; and molecular genetics of drug resistance.

Medicine Branch—
Dr. Robert C. Young

The Medicine Branch is an adult medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of the malignant lymphomas, Hodgkin's disease, breast cancer, ovarian carcinoma, sarcomas, melanoma, endometrial cancer, chronic leukemias, and testicular cancer. Training in clinical diagnostic procedures such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH, such as cancer surgery and radiation therapy. The Branch has an active autologous marrow infusion program.

The branch conducts weekly clinical conferences with the departments of radiation oncology, pathology, clinical pathology (hematology), and radiology on current problems and on the staging of lymphomas, Hodgkin's disease, and testicular carcinoma. Research focuses on the general areas of kinetics and cytogenetics of neoplastic and hemopoietic cells, immunological alterations induced by disease or chemotherapy, and the biochemical pharmacology of antineoplastic agents. In addition, an active research program is under way in the field of hormone receptors, tumor markers, and tissue culture. The branch conducts weekly laboratory conferences, in conjunction with the Clinical Pharmacology Branch, on laboratory topics of mutual interest. Collaboration with the Clinical Pharmacology Branch and other laboratory groups is maintained.

NCI- Navy Medical Oncology Branch—
Dr. John D. Minna

The NCI-Navy Medical Oncology Branch is located at the National Naval Medical Center (NNMC) in Bethesda, Maryland, across the street from the NIH Clinical Center. This branch is part of the NCI intramural Clinical Oncology Program and, with the Navy Hematology-Oncology Branch (Steven Veach, M.D., Chief), part of the NNMC cancer treatment program. The NNMC is a 450-bed tertiary referral hospital for active duty military, military retired, and military dependents. Patients are referred from around the world with all types of malignant diseases including solid tumors (e.g., lung, breast, gastrointestinal) and hematologic malignancies (Hodgkin's disease, non-Hodgkin's lymphomas, and acute and chronic leukemias). There is a large population of young adults with such malignant diseases as germ cell tumors. The program has a 30-bed inpatient service, and also provides consultation in oncology and hematology to the NNMC (approximately 40-60 active inpatients at any one time). In addition, civilian patients who are eligible for NCI studies can be admitted to the program for care and study. The NCI-Navy Medical Oncology and Navy Hematology-Oncology Branches represent a joint and integrated NCI-Navy effort in cancer patient care, clinical and laboratory investigation, and training in clinical oncology and hematology. More than 1,000 patients are followed by the oncology-hematology fellows in a study and primary care setting and each fellow has approximately 150 patients as his or her primary care responsibility. Fellows spend 6 months at the Clinical Center, NIH, and 6 months at the NNMC during the clinical year. The clinical research studies involve a wide variety of diseases and represent a collaboration between the intramural Clinical Oncology Program Branches and the NNMC.

The laboratory investigations of the branch revolve about human tumor cell biology and include studies of cell culture, somatic cell hybridization, cell kinetics, molecular biology, production of monoclonal antibodies by hybridomas, identification of tumor cell growth factors and pathways of differentiation, and human tumor cell genetics using gene transfer techniques. A major effort involves growing tumors from individual patients and selecting therapy after *in vitro* drug and radiation therapy sensitivity testing (human tumor clonogenic assay). The program is designed to include clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interest and goals.

Pediatric Oncology Branch—
Dr. Philip A. Pizzo

The Pediatric Oncology Branch conducts clinical and laboratory research activities related to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, Ewing's sarcoma and neuroblastoma. Children and adolescents are accepted for treatment. Three areas of clinical investigations are stressed: chemotherapy with new or established agents; hematologic support and bone marrow transplantation; and diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 30 inpatient beds and an extensive outpatient department. The branch also has an extremely active teaching program, with 12 weekly clinical and laboratory conferences and seminars. Candidates with prior training in internal medicine or in pediatrics may apply to this branch and are eligible for Board certification in medical oncology or pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical, surgical, and/or radiotherapeutic means, followed by experimental manipulation to prolong remission.

Comprehensive immunologic assays are performed to assess the natural history of these diseases and the influence of treatment.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. In conjunction with the Medicine Branch, a major area of interest is hematologic reconstitution through autologous bone marrow and stem cell transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised patient. These maneuvers include the use of laminar-air-flow isolation and prophylactic antimicrobial agents, as well as methods to bolster host defenses.

In the second and third year of this program, clinical research training is offered in the areas previously described. In addition to clinical research, the branch has a strong program in basic laboratory investigation with emphasis on tumor cell biology, molecular and clinical pharmacology, tumor immunology, hematopoiesis, and immunoregulation.

Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates by utilizing excellent collaborative relations with other branches of the NIH.

Radiation Oncology Branch—
Dr. Eli Glatstein

The Radiation Oncology Branch of the National Cancer Institute offers a 3-year training program in radiation oncology. This program is organized in conjunction with the Uniformed Services University of the Health Sciences, through Walter Reed Army Medical Center and the National Naval Medical Center in Bethesda. The program calls for 18 months at the NCI, 1 year at Walter Reed, and 6 months at the NNMC.

The program emphasizes all aspects of patient care in radiation therapy with major emphasis on treatment planning and dosimetry. Experimental approaches are emphasized within the National Cancer Institute as part of prospective clinical trials; conventional treatment approaches are emphasized at the military facilities. Work on radiation sensitizing compounds, radioprotecting compounds, intraoperative irradiation, and atypical fractionation schemes will be ongoing at NCI. Areas of investigation include primary breast cancer, pancreatic carcinoma, carcinoma of the esophagus, small cell carcinoma of the lung, lymphoma, Hodgkin's disease, gliomas, mycosis fungoides, soft tissue sarcomas, and pediatric neoplasms. Opportunities for study of a wider spectrum of conditions are available through the military hospitals, with special attention to head and neck cancer and gynecologic neoplasms. The emphasis at all institutions will be on combined modality approaches and on long-term follow-up to assess success and morbidity.

Preference will be shown to candidates who have completed all or part of training in another oncologic specialty. The director of training for the program is Dr. Eli Glatstein, Radiation Oncology Branch, National Cancer Institute. Interested individuals should contact him.

Surgery Branch—
Dr. Steven A. Rosenberg

This branch, a surgical oncology unit, emphasizes a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen, including sarcomas, rectal, breast, esophageal, and pancreatic cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy, as well as the development of new surgical techniques. Laboratory efforts are closely related to clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, X-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch physicians also serve as general surgeons to the entire NIH and see a variety of general surgical consultations not related to the field of cancer.

Developmental Therapeutics Program—
Dr. John Driscoll
Acting Associate Director

This program is a broadly based endeavor which promotes and supports all pertinent activities essential to preclinical development of new treatment modalities for cancer, particularly chemotherapy. A systematic search is conducted for potential antitumor agents. These are subjected to programmed preclinical evaluation according to a scheme called the Linear Array. In this approach the program is responsible for all preclinical phases of development including acquisition and synthesis of materials, isolation and production of diverse natural products, screening, pharmaceutical development, toxicology, and pharmacology.

The Office of the Associate Director is responsible for overall administration of a large intramural research program and an extramural program on preclinical development of therapeutic modalities.

Medical Staff Fellows

First-year medical staff fellows in the Clinical Oncology Program are eligible to work in the laboratories of the Developmental Therapeutics Program (DTP) for their second and third years of research training. The following paragraphs describe current projects from which medical staff fellows may elect to participate.

Laboratory of Chemical Pharmacology—
Dr. Richard L. Cysyk, Acting

This laboratory brings together scientists who play an important role in the use of pharmacologic information—plasma levels, tissue levels, mechanism of action, transport and metabolism studies—for experimental chemotherapy and earlier development and use of cancer chemotherapeutic agents for the clinic.

The pharmacologic properties of potential and established antitumor agents are evaluated *in vitro*, in animals and humans. These studies include evaluation of the antitumor activity of single agents, adjuvant and combination chemotherapy, and other modalities for cancer therapy. Other studies involve investigations on mechanism of action, structure-activity relationships, transport, dose-response relationships, effects on the immune system, mutagenic and carcinogenic potential of antitumor agents, and their disposition in laboratory animals and humans. The latter studies include the establishment of rates and rate constants that govern the passage of drugs from one body compartment to another.

Laboratory of Medicinal Chemistry and Biology—
Dr. David G. Johns

This laboratory conducts an integrated program on the development of antitumor agents. Compounds with potential antitumor activity are synthesized, and effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites, e.g., nucleic acids, nuclear proteins, microtubular protein, and enzyme systems. Analytical methodology for *in vivo* studies with new agents is developed and, where warranted, biological studies with these agents are extended to the preclinical and phase I stages. A contract-supported program to characterize the mode of action of new antitumor agents is also managed here. This laboratory stresses rapid and continuous utilization of the data generated from biological studies for elucidation of structure-activity correlations for guidance in synthesis of new antitumor agents of potential clinical value.

- Drug Design and Chemistry Section—
  Dr. John S. Driscoll

This section is involved in chemical research on the design and synthesis of new drugs for the treatment of cancer; the chemistry of therapeutic agents and drugs; the structure, purity, decomposition products and metabolites of antitumor drugs by analytical instrumental techniques; the development of structure-activity techniques to summarize existing data and provide guidelines for analog synthesis; and the promotion of an interdisciplinary approach to the synthesis and evaluation of rationally designated drugs by collaboration between chemical and biological scientists.

- Molecular Biology and Methods Development Section—
  Dr. Marco Rabinovitz

This section is developing approaches for the potentiation of cancer chemotherapeutic activities. Nutritional and pharmacological regimens are first explored in tissue culture and then extended to the tumor-bearing animal in attempts to direct cytotoxic agents toward the tumor cell and away from sensitive normal tissues. Synthesis of new cytotoxic and potentiating agents is also undertaken to achieve this goal. Biochemical studies include analysis of inhibition kinetics of binding, transport, and detoxification of cytotoxic agents in sensitive and resistant tumor cells and sensitive host tissues.

- Applied Pharmacology Section—
  Dr. Robert I. Glazer

This section is studying the action of anticancer drugs on neoplastic cells at the molecular level. Included are investigations of the drugs' effects on the synthesis and post-transcriptional processing of nuclear RNA, the *in vitro* translation of messenger RNA, and the function of nonhistone chromosomal proteins upon transcription. Characterization of target enzymes for anticancer agents is also pursued using analytical techniques such as affinity chromatography, electrophoresis, and isoelectric focusing.

Laboratory of Medicinal Chemistry and Biology—

- Drug Interactions Section
  Dr. Theodore E. Gram

This section is concerned with the biochemical mechanisms involved in the toxicity of oncolytic agents and other xenobiotics. Whenever possible, biochemical (or enzymic) and morphologic correlates are sought. The lung and penumotoxicity are of particular interest to this section. Studies have concentrated on bleomycin and paraquat at model pneumotoxins, the nephrotoxicity of oncolytic platinum agents such as cis-platin, and the cardiotoxicity of adriamycin. In all these investigations, the role of drug oxidation by the cytochrome P-450 mixed function oxidase system—either in the activation or inactivation of the toxic chemical species—is considered.

- Biochemistry Section
  Dr. David A. Cooney

The Biochemistry Section is engaged in ongoing examination of the mechanisms of sensitivity or resistance of experimental and human neoplasmas to new oncolytic drugs. Toward this end, quantitative assessments are made of the specific activities of enzymes anabolizing antimetabolites in representative tumors in the hope of developing assays predictive of antitumor response. In such studies use is made of a broad spectrum of analytical techniques, ranging from facile tritium-release enzyme assays to kinetic determinations of inhibition constants.

Laboratory of Molecular Pharmacology—
Dr. Kurt W. Kohn

Mechanisms of action of anticancer agents are studied in culture and subcellular systems with particular attention to effects involving DNA and nuclear proteins. These investigations focus on the relation between drug-induced macromolecular damage (and its repair) and cell survival. Secondly, drugs are used as probes of the structure and function of DNA and chromatin. Experimental approaches include cell culture, DNA macromolecular damage measurements, and nuclear protein fractionation techniques.

Laboratory of Tumor Cell Biology—
Dr. Robert C. Gallo

The objectives of the Laboratory of Tumor Cell Biology are to develop, implement, and analyze data obtained from studies of cell proliferation, cell differentiation, and biochemical growth characteristics of normal and malignant mammalian cells both *in vivo* and *in vitro*. Particular attention is given to hematopoietic cells, their normal behavior, and especially changes seen during leukemogenesis. Because of unusual access to human blood cells and because of the interest of this group, there is special focus on human leukemias and lymphomas. It is anticipated that an enhanced understanding of cell regulatory mechanisms will permit the optimal use of antitumor agents in the therapy of cancer and the development of new approaches.

The Laboratory of Tumor Cell Biology is concerned with several biological and biochemical problems: (1) Studies on the cellular and molecular origin and pathogenesis of human leukemia. Biochemical control mechanisms involved in cell differentiation and neoplastic transformation are examined. Tumor viruses of animals are used both as tools (to define and isolate genes and gene products important for growth in man) and to understand mechanisms of naturally occurring animal leukemias. Also, studies designed to determine if humans have similar viruses (retroviruses) are and have been intensively studied. (2) Studies on the biochemical events preceding mitosis. An understanding of these events appears essential to the control of proliferation, and information derived from such studies may lead to more effective inhibitors of neoplastic cell growth. Events leading to mitosis are also of interest since many of the effective antitumor agents are useful only when cells are in DNA replication or in mitosis. Phytohemagglutinin-stimulated human lymphocytes and tissue-cultured cells are the principal tools in these studies. (3) Attempts to develop new approaches to cancer chemotherapy using information gained from basic cellular studies. (4) Studies on the development of biochemical and immunologic markers for malignant cells are carried out. Biochemical and immunologic studies are also conducted in individuals with disorders associated with an increased incidence of neoplasia. (5) Controls regulating cell growth and differentiation, and the process of malignant transformation in hematopoietic cells. (6) Growth factors (and their receptors) that control the growth and differentiation of blood cells have been isolated and are under intensive study, e.g., T-cell growth factor (TCGF), CSF, and related hematopoietic growth effecting molecules.

NCI Informational Bulletin

Prospective applicants to the National Cancer Institute may obtain an NCI Informational Bulletin by writing Dr. Alan Rabson, Director, DCBD, NCI, Building 31, Room 3A03, National Institutes of Health, Bethesda, MD 20205.

National Eye Institute

Carl Kupfer, M.D.,
Director
Elmer J. Ballintine, M.D.,
Clinical Director

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three medical staff fellows from those candidates who have completed an accredited 3-year ophthalmology program. Fellows spend time in both clinical and laboratory research including patient care activities.

In selection of medical staff fellows, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

The National Eye Institute has developed its clinical and research program into four major branches, the Laboratory of Vision Research, the Laboratory of Sensorimotor Research, the Office of Biometry and Epidemiology, and the Clinical Branch.

Office of Biometry and Epidemiology—
Fred Ederer

The Office of Biometry and Epidemiology conducts studies that tend to fall into the broad areas of clinical trials and natural history, on the one hand, and epidemiology on the other.

The clinical trials section is now responsible for three national multiclinic trials involving vitrectomy, drugs, and photocoagulation, as treatments to prevent progression in patients with diabetic retinopathy. These studies include thousands of patients, and combine the skills of several disciplines, including clinical, statistical, and computer sciences. Data generated in these studies not only provide a base for treatment strategies, but permit investigation of the extent to which risk factors other than treatment are related to disease progression.

The epidemiology section generates data on the prevalence, incidence, and distribution of diseases of the eye. Such data are used to evaluate hypotheses on the causes of such diseases. Data sets from the Framingham Eye Study and the Health and Nutrition Examination Survey are being actively analyzed to explicate the risk factors for changes in the lens and retina. A major national study of the prevalence of visual acuity impairment and its causes will soon be under way.

Laboratory of Vision Research—
Dr. Jin Kinoshita

The laboratory is engaged in research involving the following disciplines:

Biochemistry—This section conducts studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolism of photoreceptors are also under investigation. In addition, synthesis of sugar-containing polymers in the retina are being studied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

Experimental Embryology—This section identifies and characterizes the myriad tissue interactions that control orderly growth of the vertebrate eye and assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ. Because most congenital defects of the eye are attributable to interference with hese interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. Researchers are determining which tissues are responsive o such influences, the duration of these potencies and competencies during embryogenesis, the specificities of these ineractions, and the nature of interactions which control morphogenesis.

Particular attention is being focused on newly discovered, cellfree, collagen-containing "initiator layers" which are ransiently produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of he body.

Experimental Pathology—Research beng conducted in this section centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of inraocular pressure on eye tissue, the damaging effect of light on the retina, aser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

Neurophysiology—Investigations on he cellular organization underlying visual perception are currently under way in his section. Studies are being conducted on the responses of single nerve cells at various levels in the visual nervous ystem of mammals. The purpose of this work is to understand how nerve cells ontribute to visual sensations such as olor, shape, movement, and depth. The echnique employs fine microelectrodes which can be inserted into the brain in order to record from single nerve cells. It uses refined optical methods to enable an xperimenter to stimulate the retina with pots or slits of colored lights whose movement and shape can be quantitatively controlled. It involves electrophorescing dye into single cells whose responses have been studied and then finding these ells within the brain or retina.

By this means both structure and function of nerve cells can be correlated and the underlying circuitry of the visual system understood. This approach requires close interaction between single cell physiology and cellular anatomy at the light and electron-microscopic level.

Retinal and Corneal Metabolism—This section is investigating the function of the retina, pigment epithelium, and cornea in relation to clinical diseases such as retinitis pigmentosa and keratomalacia.

The mechanism by which visual cells detect light and produce neural messages is not known. Calcium may play a role in the process since it mimics the effects of light on the retina and is found in very high concentrations in pigment epithelium and retinal photoreceptors. Small intracellular messengers called cyclic nucleotides have also been found in extraordinarily high concentrations in retinal photoreceptors. Since light markedly affects their concentration, they, too, are probably intimately involved in the visual process. A method of injecting various substances into visual cells is now being developed to determine directly the effect of these substances on the visual process in both normal and pathologic conditions.

Studies on the synthesis and degradation of the visual protein rhodopsin have helped explain how retinal photoreceptors are renewed. Defects in this process may underlie some forms of retinal degeneration; thus, studies using dystrophic retinas of test animals are under way to compare the process of photoreceptor renewal in normal and pathologic conditions. Substances such as hormones and neurotransmitters that affect the normal growth and development of retinal cells in tissue culture are being assessed. Several have already been identified and are being further studied in relation to their role in retinal function.

Specific receptor molecules for vitamin A have been found in retina and pigment epithelium. These receptors are probably involved in the normal uptake, distribution, and retention of the vitamin in the visual system. Differences in receptor concentrations in retinas of normal humans and patients with retinitis pigmentosa have been found.

Vitamin A receptors are also present in the cornea and conjunctiva. The possible relationship of these receptors to corneal disease is being considered. Other aspects of corneal physiology, such as glutathione metabolism, are under investigation. Such studies are important not only for understanding corneal function and transparency but for improving corneal transplant and surgery techniques as well.

Laboratory of Sensorimotor Research—
Dr. Robert Wurtz

This laboratory conducts research on the central neural bases of vision and eye movements in the primate, and the application of these results to clinical problems in patients with visuomotor deficits. The laboratory uses a multidisciplinary approach, availing itself of techniques of neurophysiology, neuroanatomy, experimental psychology, psychophysics, systems engineering, and computer science.

One series of projects is designed to elucidate the central neural mechanisms in the control of visually guided eye movements. The activity of single neurons in cortical and subcortical areas is recorded using microelectrodes placed in the brains of behaving animals, in order to analyze the relationship of neural events to eye movements and the presentation of visual stimuli. Quantitative studies of eye movement are performed in animals with lesions in those brain areas which physiological recordings have indicated may be important in the neural mechanisms underlying eye movement and visual perception. The anatomic connections of these areas of interest are studied using axoplasmic transport methods.

A second series of experiments investigates the visual processing underlying visual perception. These experiments correlate the discharge of single cells within cortical and subcortical regions of the brain with the stimulus presented to the monkey.

In another series of studies the vestibulo-ocular system is used as a tool to study the mechanism by which the brain can adjust to environmental changes. This adaptive plasticity is studied using systems analysis of single neuron discharge patterns recorded from performing animals, and analysis of the performance of monkeys, normal human subjects, and patients with oculomotor deficits.

The ability of patients with visuomotor deficits is studied using paradigms for performance that have been developed using normal humans and monkeys, in order to study residual abilities following damage to discrete brain areas, and to develop strategies for rehabilitation of brain-damaged patients.

Since recent advances in sensorimotor physiology and psychophysics have been made possible by developments in the application of the online laboratory computer to these problems, a significant effort in the laboratory is the development and refinement of computer methods for the control and analysis of experimental results.

Laboratory of Molecular and Developmental Biology—
Dr. Joram Piatigorsky

This laboratory conducts basic research on cellular and molecular biology. Emphasis is given to molecular and developmental genetics. The research is designed to elucidate both normal and disease processes. Particular attention is given to hereditary diseases which can be studied at the gene level. Much (but not all) of the work uses eye tissues as models for general problems concerning cellular differentiation and gene expression. Normal and pathogenic visual processes are also being related to the structure and function of genes.

Three major gene families are currently being investigated; namely, crystallins, opsins, and collagens. DNA clones are being constructed, analyzed, and used as probes for understanding a variety of normal and pathogenic circumstances. Phospholipid metabolism—particularly at the cell membrane—is also under investigation in order to advance our knowledge of cellular differentiation and differential gene expression.

Clinical Branch—
Dr. Elmer J. Ballintine

The branch plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of visual system disorders. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the branch's responsibility to investigate the causes and prevention of visual impairment.

- Cataract Section—
  Dr. Jin Kinoshita

Cataracts of unusual origin and congenital cataracts are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

- Section on Neuro-ophthalmology—
  Dr. David B. Cogan

Patients from the ophthalmic and neurologic services are being studied using advanced methods for electro-oculography, pupillometry, videotape recording, and computer analysis. The main emphasis of these studies is on cerebellar disorders that affect ocular movements.

- Section on Glaucoma—
  Dr. Douglas E. Gaasterland

Intraocular fluid dynamics in normal and glaucomatous eyes and their alteration by pharmacologic agents are being studied. A controlled clinical trial to test the value of early treatment of ocular hypertension is under way. Innovative surgical techniques are being assessed in selected cases of primary, secondary, and congenital glaucoma and in cases in which antiglaucoma surgery has failed. The properties of trabecular meshwork are being studied in tissue culture.

- Section on Ophthalmic Genetic Studies—
  Dr. Muriel I. Kaiser

These include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogenesis of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

The pathogenesis of unusual types of congenital or developmental anomalies of the eye is being studied under protocol. These cases include pigment dispersion syndrome, progressive essential iris atrophy, oculocutaneous albinism and abnormalities of the anterior chamber angle associated with glaucoma.

- Section on Retinal and Ocular Connective Tissue Diseases—
  Dr. David A. Newsome

Retinal deteriorations—Clinical, biochemical, cell biological, and metabolic investigations are being conducted to define underlying mechanisms in diseases such as senile macular and related degenerations and the maculopathy of retinitis pigmentosa. Macular edema is also of special interest. The retinal pigment epithelium, its normal function, pathophysiology, and interrelationships are of special interest. Family studies of macular and retinal degenerations are emphasized.

Vascular diseases—Clinical investigations are being conducted in the treatment and underlying mechanisms of diabetic retinopathy.

Ocular connective tissues—Characterization and purification of extracellular matrix molecules synthesized by normal and abnormal ocular tissues, immunofluorescent antibody studies, and the enzymology and immunology of corneal melting are being investigated actively.

- Section on Ophthalmic Pathology—
  Dr. Merlyn Rodrigues

Surgically excised biopsy material and eyes obtained from autopsies or enucleations performed at the Clinical Center are processed and studied by light and electron microscopy. Many of these specimens are from subjects with unusual metabolic and genetic diseases, glaucoma, and retinal disorders. Some of these specimens are further investigated by immunohistochemical techniques. The ocular effects of diabetes in animals, S-antigen uveitis, and chemotaxis induced by synthetic mediators have been studied in collaboration with investigators from other Institutes at NIH. There is also opportunity for research on corneal diseases and glaucoma and for further investigation of mediators of ocular inflammation and animal models of diabetes.

A 2-year training program in clinical and experimental eye pathology is available under the supervision of Drs. Cogan, Kuwabara, and Rodrigues. This program includes experience in histochemistry and electron microscopy.

- Section on Ocular Immunology—
  Dr. Robert B. Nussenblatt
  Immunologic mechanisms relating to ocular inflammatory disease are being studied. The possible role of ocular autoimmunity in uveitis is being actively investigated. Patients with posterior uveitis, i.e., toxoplasmosis, pars planitis, birdshot choroidopathy, and sarcoid are being sought in order to evaluate their immunologic responses. The evaluation of patients with ocular inflammatory disease also includes monitoring their ocular physiologic responses during disease and when the inflammation is quiescent. The relationship of HLA and the immunologic response of ocular inflammatory patients to antigens is being looked at, as are other immunologic factors, such as antibody production, suppressor cell activity, and macrophage responsiveness. Patients are in addition being sought for a controlled double masked study in the therapy of ocular toxoplasmosis.

National Heart, Lung, and Blood Institute

Peter L. Frommer, M.D.,
Acting Director
Jack Orloff, M.D.,
Director of Intramural Research
Harry R. Keiser, M.D.,
Clinical Director

Candidates for research and clinical positions as medical staff fellows have only one interview in this Institute. Medical staff fellows are interviewed by a committee made up of the director of intramural research, the clinical director, and the deputy clinical director. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the National Heart, Lung, and Blood Institute (NHLBI). After appointment and prior to entering on duty each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the fellow and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. On the basis of past experience, it appears virtually certain that each fellow will be able to work with the group of his or her choice. The level of research responsibility and freedom will depend upon the fellow's training and experience as well as desires.

Each medical staff fellow will devote time primarily to research in the laboratory under the supervision of a preceptor in the area of selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of the laboratory.

All appointments as medical staff fellow are for a minimum of 2 years with a third optional year. In the past, most fellows have elected to remain for 3 full years and have been accorded this privilege.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research. Candidates must have satisfactorily completed a minimum of 2 years of residency training in general internal medicine in a program approved by the American Board of Internal Medicine by the starting date of their appointment. The first year of the clinical fellowship will be credited as a third year of training in internal medicine by the American Board of Internal Medicine if the candidate's clinical competence was satisfactory during the previous 2 years of training and is satisfactory here.

Medical staff fellows will be responsible, under the guidance of investigators on the NHLBI staff, for the primary medical care of research patients during 10 to 12 months of the first year of their service. During this time they will rotate through the four medical services that serve the clinically oriented branches of the Institute and assist in the work of the service with consultations and in the outpatient department. These services occupy 75 beds and include cardiology, hypertension-endocrinology, lung, and hematology and metabolism.

The clinical period is one of intensive training under direction of the clinical director and staff. It offers exposure to case material of extraordinary range and to highly sophisticated approaches to investigation of disease.

The fellow devotes both time off the wards and a full 12-14 months of the 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either clinical or nonclinical.* No clinical responsibilities are required during the second or the optional third year for fellows who have chosen nonclinical laboratories.

Medical Staff Fellows in Surgery

The Surgery Branch appoints four to five fellows in surgery for a 2-year period beginning each July 1. The program is designed for young surgeons with primary interests in cardiovascular surgery and cardiovascular physiology. In making appointments, preference will be given to candidates contemplating a career in research or academic medicine. Candidates must have completed an internship and at least 1 year of surgical residency by the starting date of their appointment. Candidates interested in this possibility and desiring additional information are encouraged to write to Dr. Andrew G. Morrow, Chief, Surgery Branch, NHLBI, Bldg. 10, Room 6N242, NIH, Bethesda, MD 20205.

Appointments in Laboratory Research

These appointments are designed to give highly qualified physicians an opportunity to do either clinical or basic research in any area of the Institute under the direct supervision of an experienced preceptor. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises.

Staff Appointments

Laboratories with the NHLBI sometimes have openings for medical staff fellows appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Checklist for the Institute. Selections for those positions are made by the chief of the branch or laboratory.

Medical Staff Fellows in Epidemiology

The Epidemiology Branch conducts population-based studies on the occurrence and natural history of cardiovascular, cerebrovascular, blood, and obstructive pulmonary diseases in general and selected populations in the United States and foreign countries. Through clinical examinations and analyses of available data, these studies seek to improve knowledge of the personal, environmental, and familial factors underlying these disorders. One or two candidates are chosen each year for 2-year assignments in Bethesda or for one of the field programs. The fellowships may begin after internship or after 1 year of training in a clinical residency or school of public health. Interested candidates are encouraged to write to Dr. Manning Feinleib, Chief, Epidemiology Branch, NHLBI, Bethesda, MD 20205, for more detailed information about specific assignments.

Joint Endocrinology Training Program

Medical staff fellows from the NHLBI may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to quality fellows for the Endocrinology Subspecialty Boards. NHLBI participants will spend an additional 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the fellow will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the fellow's 3 years will be spent primarily in research activity within the NHLBI, although he or she will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two NHLBI fellows to enter this program in any one year.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Medical staff fellows are expected to take advantage of this academic work. (See part 4, page111.)

Clinical Research Branches

Cardiology Branch—
Dr. Stephen E. Epstein

- Section on Cardiovascular Diagnosis— Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by various cardioactive agents, with particular emphasis on calcium antagonists.

- Section on Experimental Physiology and Pharmacology—
  Dr. Stephen E. Epstein

Research is aimed toward understanding the physiologic, anatomic, and biochemical mechanisms responsible for control of the normal heart and circulation, elucidation of the alterations produced by ischemic and nonischemic heart disease, and evaluation of interventions designed to reverse the biochemical and, thereby, the physiologic aberrations of function. Several approaches are being employed to achieve the above, including hemodynamic, echocardiographic (one- and two-dimensional systems), and radionuclide studies in man, electron-microscopic and biochemical studies of tissues obtained from human and animal surgical specimens and pharmacological investigations in man and animals. A major interest is the study of calcium antagonist drugs.

- Section on Molecular Cardiology—
  Dr. Robert S. Adelstein

Current investigations are directed toward understanding the function and regulation of contractile proteins in muscle and nonmuscle cells. The role of cyclic nucleotides, calcium, calmodulin, and myosin phosphorylation in regulating actin-myosin interaction is of particular interest. Projects include myosin phosphorylation and the regulation of kinases and phosphatases in smooth muscle, heart, and nonmuscle cells such as brain, blood platelets, and myoblasts. The role these proteins play in cellular development, differentiation, and tumorigenicity is of current interest.

Clinical Hematology Branch—
Dr. Arthur W. Nienhuis

The research activities in this branch, while diverse, are generally focused on the problems of red cell production, hemoglobin synthesis, and hemoglobin function. Specific monoclonal antibodies produced by hybridoma cells are being characterized with respect to their reactivity with hematopoietic stem cells. These antibodies will be used to purify stem cells, thereby facilitating their functional and biochemical characterization and also to correlate stem cell number with function in patients with various bone marrow failure syndromes. The regulation of several globin genes is being studied in the context of developmental switches in hemoglobin phenotypes in man and other species. Furthermore, the study of gene expression in patients with thalassemia is directed toward definition of the molecular defects which result in deficient hemoglobin synthesis in these syndromes. Various strategies are being devised and tested with the long-term goal of introducing functional genes into the erythroid cells of such patients. Experimental strategies directed toward treatment of severe aplastic anemia, iron overload secondary to chronic transfusion, and sickle cell anemia are under investigation.

Hypertension-Endocrine Branch—
Dr. Harry R. Keiser

This branch represents a merger of the former Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension; activities are wide-ranging, as indicated by the description of section activities.

- Section on Experimental Therapeutics—Dr. Harry R. Keiser

A wide spectrum of research opportunities is offered, ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of the kallikrein-kinin system, renin-angiotensin-aldosterone system, prostaglandins and catecholamines and their interactions, conducted both in man and in experimental animals. Other studies encompass disorders of serotonin, histamine, and peptides.

- Section on Biochemical Pharmacology—
  Dr. Walter M. Lovenberg

This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of enzymes responsible for the biosynthesis of neurohumoral amines. The role of these systems in disease states, particularly hypertension, is of prime interest, and investigations are extended from the molecular level to experimental animals and man.

Molecular Disease Branch—
Dr. H. Bryan Brewer

The research activities of this branch are directed toward the elucidation of the molecular mechanisms involved in lipid transport and metabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis. Studies take several approaches employing protein chemistry, immunology, tissue culture, molecular biology, and enzymology. Clinical research is focused on the effects of drugs and therapeutic diets on dyslipoproteinemia and on kinetic analysis of the metabolic defects in patients with these diseases. Activities are integrated in such a way that, if medical staff fellows wish, they may participate in collaborative research involving several different areas.

Pathology Branch—
Dr. William C. Roberts

This branch is concerned with the study of morphologic aspects of cardiovascular and pulmonary diseases and their correlation with functional derangements. Morphologic analyses include transmission and scanning electron microscopy.

Pulmonary Branch—
Dr. Ronald G. Crystal

Research in this branch is designed to investigate the structure and function of the lung in health and disease through cellular and biochemical methods. Both laboratory and clinical investigations are conducted. Techniques of protein chemistry, molecular biology, tissue culture, and immunology are used. Emphasis is placed on the regulation of synthesis and degradation of connective tissue and on the inflammatory and immune processes in the normal and diseased lung. Clinical research is directed toward correlating physiologic, biochemical, immunologic, and morphologic observations in patients with interstitial lung disease, destructive lung disease, hereditary disorders of connective tissue, hypersensitivity lung disease, and other lung disorders with an immunologic basis.

Surgery Branch—
Dr. Andrew G. Morrow
(See page 35, Medical Staff Fellows in Surgery.)

Basic Research Laboratories

- Section on Theoretical Biophysics—
  Dr. John L. Stephenson

The primary interest of this section is the theory of transport processes in biological systems, with particular reference to problems in cardiovascular, renal, and membrane physiology. The section is concerned with the formulation of theoretical models and the development of mathematical and computational methods for their analysis. Currently, much of the research centers on the mechanism of urine formulation in the mammalian kidney and theoretical aspects of epithelial transport of electrolytes and water.

Laboratory of Biochemical Genetics—
Dr. Marshall Nirenberg

- Section on Molecular Biology—
  Dr. Marshall Nirenberg

This section is primarily concerned with basic biochemical studies pertaining to the transfer of genetic and neural information, for example, genetic programs for differentiation that determine informational reactions of neurons. Systems and problems involve the culture of mammalian cells and hybrid cells. Studies are also done on gene function for informational molecules such as enzymes of transmitter metabolism receptors, membrane ionophores, cyclic nucleotides, and other components required for cell recognition and communication.

- Section on Macromolecules—
  Dr. Alan Peterkofsky

This section is concentrating on studies of cellular control mechanisms. One area of interest involves the hypothalamic tripeptide thyrotropin-releasing factor. The biological properties of some new derivatives of thyrotropin-releasing factor are under investigation. Another focus of attention is the control of the synthesis

understanding protein-ligand interactions, protein-protein interactions, and enzyme

INDEX MATRIX

The matrix is intended to serve as a guide to programs which offer medical staff fellows clinical experience in the areas listed. The matrix is not a comprehensive list of programs. Check the index at the back of the catalog for programs in other research areas that may not be listed here.

	AGING	ALLERGY	ANATOMICAL PATHOLOGY	BLOOD BANKING	CARDIOLOGY	CLINICAL PATHOLOGY	DENTISTRY
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ransfer proteins, such as selenoproteins, erridoxins, flavoproteins, and sulfhydryl roteins.

- Section on Protein Chemistry—
  Dr. Ann Ginsburg

Studies on protein structure in this aboratory are directed toward

tron transport chain of *Escherichia coli* are presently being investigated.

- Section on Organelle Biochemistry—
  Dr. Martin Flavin

This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the

vestigations are extended from the molecular level to experimental animals and

clude transmission and scanning electron microscopy.

DERMATOLOGY	DIABETES	ENDOCRINOLOGY	EPIDEMIOLOGY	GASTROENTEROLOGY	GENETICS	GYNECOLOGY	HEMATOLOGY	IMMUNOLOGY	INFECTIOUS DISEASES	MEDICAL ONCOLOGY	METABOLISM	MICROBIOLOGY	NEUROLOGY	NEUROSURGERY	NUCLEAR MEDICINE	NUTRITION	OBSTETRICS	ONCOLOGY	OPHTHALMOLOGY	PEDIATRIC ONCOLOGY	PEDIATRICS	PHARMACOLOGY	PSYCHIATRY	PSYCHOPHARMACOLOGY	PULMONARY	RHEUMATOLOGY	SURGERY	SURGICAL ONCOLOGY
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mammalian kidney and theoretical aspects of epithelial transport of electrolytes and water.

Laboratory of Biochemical Genetics—
Dr. Marshall Nirenberg

- Section on Molecular Biology—
  Dr. Marshall Nirenberg

This section is primarily concerned

Dr. Alan Peterkofsky

This section is concentrating on studies of cellular control mechanisms. One area of interest involves the hypothalamic tripeptide thyrotropin-releasing factor. The biological properties of some new derivatives of thyrotropin-releasing factor are under investigation. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells.

Laboratory of Biochemistry—
Dr. Earl R. Stadtman

- Section on Enzyme Mechanism and Metabolic Regulation—
  Dr. P. Boon Chock

This section conducts biophysical studies on various enzymes and proteins with emphasis on the mechanism of enzyme action and its regulation. Currently, we are investigating the roles of covalent modification in metabolic regulation of enzymes. This involves the study of *Escherichia coli* glutamine synthetase cascade. In addition, mechanistic studies are being carried out for the activation of cyclic nucleotide phosphodiesterase by calmodulin, glutamine synthetase catalysis, and glutamine synthetase antibody-antigen interaction.

- Section on Enzymes—
  Dr. Earl R. Stadtman

This group studies diverse enzyme systems that offer unique opportunities to elucidate basic biochemical phenomena, namely, those concerned with vitamin-coenzyme function, the cellular regulation of metabolism, the energy-dependent transport of metabolites across membrane barriers, and mechanisms of enzyme action.

- Section on Intermediary Metabolism and Bioenergetics—
  Dr. Thressa C. Stadtman

This section is concerned primarily with investigations on the mechanisms of anaerobic amino acid dissimilation and phosphorylation coupled with anaerobic electron transfer processes. Special emphasis is on the roles of various coenzymes (vitamin B_{12}, coenzyme, CoA, pyridoxal phosphate, flavins, pyridine nucleotides, lipoic acid, and naphthoquinones) and of various electron ransfer proteins, such as selenoproteins, ferridoxins, flavoproteins, and sulfhydryl proteins.

- Section on Protein Chemistry—
  Dr. Ann Ginsburg

Studies on protein structure in this aboratory are directed toward understanding protein-ligand interactions, protein-protein interactions, and enzyme catalysis and regulation.

Laboratory of Cell Biology—
Dr. Edward D. Korn

This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

- Section on Cellular Biochemistry and Ultrastructure—Dr. Edward D. Korn

This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the molecular and ultrastructural basis of cell motility. Cytoplasmic actin, myosin, and related proteins are purified from nonmuscle cells and their interactions studied and compared to their muscle counterparts. Currently, emphasis is on the regulation of action polymerization, the regulation of actin-activation of myosin-ATPase, and the characterization of multiple myosins in a single cell. Opportunities are available for research and training in biochemistry and electron-microscopy.

- Section on Cellular Physiology—
  Dr. Evan Eisenberg

This section conducts studies on the molecular events of muscle contraction including the interaction of actin and myosin with each other and with the control proteins, tropomyosin, and the troponins. Emphasis is on kinetic studies with pure proteins.

- Section on Membrane Enzymology—
  Dr. Richard Hendler

This section studies enzyme systems that require organization on, or interaction with, membranes in order to ensure their proper functioning. The synthesis of DNA by enzyme complexes and the electron transport chain of *Escherichia coli* are presently being investigated.

- Section on Organelle Biochemistry—
  Dr. Martin Flavin

This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the

physiologic regulation of assembly and function. At this time the major emphasis is on the mechanism of polymerization of microtubules in brain and unicellular organisms.

Laboratory of Cellular Metabolism—
Dr. Martha Vaughan

- Section on Metabolic Regulation—
  Dr. Martha Vaughan

Research concerns mechanisms of hormone action with emphasis on the enzymes involved in synthesis and degradation of cyclic nucleotides.

- Section on Cellular Pharmacology—
  Dr. Michael A. Beaven

Research centers on the release of histamine, serotonin, and other factors during inflammatory and allergic reactions, the enzymes participating in the synthesis and degradation of these substances, and the effect of anti-inflammatory agents on cell proliferation and chemotaxis.

- Section on Biochemical Physiology—
  Dr. Vincent C. Manganiello

Research is concerned with the action of certain peptide hormones, glucocorticoids, and prostaglandins on growth and function of mammalian cells, especially cultured cells.

- Section on Molecular Mechanisms—
  Dr. Joel Moss

Research is concerned with the molecular basis for regulation of enzymes involved in cyclic nucleotide metabolism, e.g., subunit structure, covalent modification, and effector interactions.

Laboratory of Chemical Pharmacology—
Dr. James R. Gillette

- Section on Drug-Enzyme Interaction—
  Dr. James R. Gillette

The interests of this section center on various aspects of drug disposition including pharmacokinetics and the relationship between drug metabolism and drug toxicity. Its main objectives have been understanding the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

- Section on Physiology—
  Dr. Harriet M. Maling

This section studies interactions of drugs, particularly the mechanisms by which various treatments may alter the hepatotoxicity or pulmonary toxicity induced by various organic compounds. It includes studies on the relationship between hepatotoxicity and covalent binding of metabolites to liver lipids and proteins, the formation of lipid peroxides, and effects on microsomal enzymes. It also includes studies of toxicity modifications produced by treatments that alter substantially the body clearance of a compound.

- Section on Drug-Tissue Interaction—
  Dr. Gopal Krishna

This group is involved in the study of the initial events occurring in cells as the result of a variety of drug-hormone cell interactions, including the role of cyclic nucleotides as mediators of a variety of hormone actions. Recently, this section has become involved in the investigation of the biochemical mechanisms that may be involved in drug-induced tissue lesions.

Laboratory of Chemistry—
Dr. Henry M. Fales

This laboratory conducts research on methods for the structural analysis of organic compounds and investigates their biological function. Specialties are mass spectrometry, nuclear magnetic resonance, X-ray crystallography, advanced chromatography, advanced chromatographic methods, radioimmunoassay, and data retrieval techniques. Collaborative studies are carried out with other chemists, clinicians, and biologists.

- Section on Physiological Chemistry—
  Dr. John J. Pisano

The Section on Physiological Chemistry studies normal and pathological states in man at the molecular level. Under investigation are biologically active peptides (vasoactive and neuroactive), precursor proteins of the peptides, and the enzymes involved in their biosynthesis and degradation. Modern analytical techniques such as gas chromatography, high-performance liquid chromatography, affinity chromatography, mass spectrometry, and radioimmunoassay are commonly employed. Research is currently directed to the study of hypertension, new factors regulating coagulation and fibrinolysis, micro methods for the detection and the amino acid sequence analysis of polypeptides, and the discovery of naturally occurring biologically active peptides using a variety of bioassay techniques.

- Section on Chemical Structure—
  Dr. Henry M. Fales

This group isolates and identifies biochemically important and structurally interesting organic compounds using gas, liquid, high-pressure, and thin-layer chromatography in conjunction with mass spectrometry, nuclear magnetic resonance, and X-ray crystallography. The section also develops and extends methodology in above fields. Typical applications include drug metabolites, acidic components of urine in diseased states, analysis of cardiovascular drugs, insect and plant toxins, and synthetic intermediates.

- Section on Structural Nuclear Magnetic Resonance—Dr. Robert H. Highet

The section emphasizes the development and use of new techniques to study the structure and chemical characteristics of compounds of biological interest. The structure of metabolites of steroidal drugs and alkaloidal toxins and the factors influencing aromatic-alicyclic tautomerism are typical areas for investigation.

Laboratory of Kidney and Electrolyte Metabolism—
Dr. Maurice B. Burg

- Section on Electrolyte Transport—
  Dr. Jack Orloff
- Section on Renal Mechanisms—
  Dr. Maurice B. Burg
- Section on Membrane Metabolism—
  Dr. Joseph S. Handler

This laboratory conducts research on the mechanism and regulation, hormonal and otherwise, of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, toad bladder, and erythrocytes. Electrophysiology and intermediary metabolism as related to transport are emphasized.

Laboratory of Molecular Hematology—
Dr. W. French Anderson

This laboratory is concerned with investigation into the mechanism and regulation of mammalian gene expression and protein synthesis. Areas of research include molecular cloning of globin and other genes, cellfree transcription of cloned genes, gene transfer of globin (and other) genes by physical microinjection and cellular transformation techniques, regulation of protein synthesis in reticulocyte lysates studies on globin gene expression using mouse erythroleukemia cells and somatic cell hybrids. Joint studies are also carried out with the Clinical Hematology Branch.

Laboratory of Technical Development—
Dr. Robert L. Bowman

This laboratory conducts research on instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicromethods to practical clinical instrumentation.

- Section on Biophysical Instrumentation—Dr. Robert L. Berger

This section develops methods and instruments based on new physical and computer science technology to measure reaction kinetics, molecular structure, and chemistry of substances of biomedical interest. Current work involves developing calorimetric, Mossbauer spectroscopic, laser photolysis, fast spectroscopic, and fluorometric systems.

- Section on Pulmonary and Cardiac Assist Devices—
  Dr. Theodor Kolobow

This section conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This includes the development of improved blood oxygenators, blood pumps, and control systems.

National Institute on Aging

Robert N. Butler, M.D.,
Director
Richard C. Greulich, Ph.D.,
Scientific Director
Reubin Andres, M.D.,
Clinical Director

Medical Staff Fellows

The Intramural Research Program of the National Institute on Aging (NIA) is located at the Gerontology Research Center in Baltimore, MD. The clinical research program of the Laboratory of Neurosciences is located at the NIH Clinical Center, Bethesda, MD.

The multidisciplinary program of the center, located on the campus of Baltimore City Hospitals, offers 2-year clinical and basic research training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, medical staff fellows may participate in clinical activities of the Baltimore City Hospitals and the nearby Johns Hopkins Hospital. Two-year fellowship appointments may be extended in special instances to 3 years. On occasion, such extended programs, which include clinical experience, may serve to qualify the individual for certification by a subspecialty board, such as endocrinology.

In addition to the 2-year appointment a 3-year program of clinical and research training in collaboration with the division of cardiology, department of medicine, Johns Hopkins University, or the department of medicine, Baltimore City Hospitals, is offered to a limited number of candidates each year. Under this program, the fellow spends the first year in clinical training as a resident physician or clinical fellow in one of the above departments. The second and third years are spent in clinical or laboratory research on gerontology at the center. Medical staff fellows are encouraged to participate in seminars conducted by the NIA center's staff who present a comprehensive view of research in aging. Weekly research conferences are presented by staff members and invited lecturers.

A primary resource for clinical investigation on human subjects is the Baltimore Longitudinal Study of Aging. The subjects are volunteers, 20 to 96 years old or more, who reside in the community, who return for extensive studies every 1 to 2 years, spend 2½ days as inpatients each visit, and are enrolled for their entire lives. The study on men is now of 24 years' duration and involves 650 active participants; the study on women began in 1978 and its size will eventually be comparable to the male sample. The female cohort currently numbers 350 women. Medical staff fellows share in the examination of these participants.

In support of its research program, the center maintains extensive animal colonies to provide rats, dogs, and rabbits of known age, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment and photography and arts services. Computer facilities are also available, and instruction in the use of computers for laboratory research is provided. The library of the center contains one of this country's most extensive collections of literature on aging research as well as standard scientific journals.

Prospective candidates wishing further information should write to either Dr. Richard C. Greulich, Scientific Director, or Dr. Reubin Andres, Clinical Director, c/o the NIA Gerontology Research Center, Baltimore City Hospitals, 4940 Eastern Avenue, Baltimore, MD 21224.

Clinical Research Branches

Clinical Physiology Branch—
Dr. Reubin Andres

This branch is primarily concerned with studies on physiologic changes occurring over the entire adult lifespan. Studies include the quantification of age changes, elucidation of mechanisms underlying these changes, and relationships between aging processes and specific disease states.

- Endocrinology Section—
  Dr. Robert I. Gregerman

This section conducts studies on the molecular basis of age-related changes of hormone responses, especially those related to the biochemistry of the adenylate cyclase system and hormone receptors; aging and the endocrinology of the reproductive system; and the enzymology and peptide chemistry of the renin-angiotensin system. Clinical studies are conducted on subjects from the Baltimore Longitudinal Study of Human Aging. Studies on rodents are done on a variety of organs; hormone studies are done in animals of all ages.

- Cardiovascular Section—
  Dr. Edward G. Lakatta

Scientists in this section investigate cardiovascular hemodynamic function in man using noninvasive methods that include studies both in normal and cardiovascular disease states. Studies on isolated cardiac muscle focus on the mechanisms that govern excitation-contraction coupling. Additional studies investigate the effect of age, hypertrophy, and physical conditioning on electrophysiological, contractile, and biochemical parameters in cardiac muscle. Response to stress such as hypoxia and adrenergic stimulation and other pharmacological interventions are also studied in these animal models.

- Metabolism Section—
  Dr. Reubin Andres

This section emphasizes research on glucose homeostasis and its endocrine control. Factors controlling insulin secretion, including gastrointestinal insulinotropic hormone, are quantified with the use of the servo-control glucose clamp technique. Clinical investigations in man are concerned with the assessment of interrelations among such variables as age, obesity, diabetes mellitus and its complications, hemoglobin Al, serum lipids, dietary factors, and physical activity. Biologic rates of aging in multiple systems are also assessed. The isolated perfused rat pancreas preparation supplements human studies.

- Clinical Immunology Section—
  Dr. William H. Adler

Studies are conducted on the decline in host immune responsiveness that is seen in aging. These studies involve the development of diagnostic procedures for the detection of relative immunodeficiencies in humans and the investigation of the mechanisms of these deficiencies in humans and experimental animals.

- Human Performance Section—
  Dr. Jordan D. Tobin

This section supports the Baltimore Longitudinal Study of Human Aging with work in a variety of areas. Body composition studies seek the causes of tissue loss in the aged. Exercise physiology research is designed to determine the causes of reduced physical capacity in old age. Habitual physical activity and nutrition of subjects are monitored. Assessments are made of neuromuscular function, psychomotor capacity, hearing, and vision. Pulmonary physiology is studied in the context of genetic and environmental factors. Other work includes studies of the relationship of blood pressure to psychomotor variables and intelligence; dermatoglyphics in disease, world populations, twins, and aging; and the factors underlying reduced sexual function in the elderly.

Laboratory of Neurosciences—
Dr. Stanley I. Rapoport

The laboratory's clinical program investigates cerebral metabolism in man in relation to aging and dementia. The laboratory also examines pharmacokinetics and peripheral metabolism of centrally acting drugs as a function of age.

- Section on Brain Aging and Dementia
  Dr. Neal R. Cutler

At NIA's Section on Brain Aging and Dementia, located at the Clinical Center of the National Institutes of Health in Bethesda, MD, clinical scientists are involved in research activities focused primarily on dementias and associated neuropathologic diseases as these relate to the elderly. Studies look closely at multi-infarct, Alzheimer's type senile dementia, and Parkinson's disease. The section also examines the normal aging process from a biochemical, cardiovascular, and general physiologic perspective which includes a careful evaluation of brain function. Newest technologies, such as positron emission tomography (PET), are employed to look at brain metabolism in aging and dementia.

Particular attention is paid to the careful clinical evaluation of the noradrenergic and dopaminergic systems, through the use of biochemical and pharmacological explorations, in the areas of normal aging, essential hypertension, and related disorders.

The clinical pharmacology of aging is another major area of interest for our clinical program, and includes the careful evaluation of the pharmacokinetics and pharmacodynamics of various antihypertensive and central nervous system agents in the elderly.

In addition, there is a major interdigitation between basic laboratory investigations of cerebral metabolism and neuropharmacology.

Basic Research Laboratories

Office of the Scientific Director

- Comparative Nutrition Section—
  Dr. Charles H. Barrows

Scientists investigate the relationship between aging and nutrition in animal populations. The specific areas studied include the effects of age on absorption, distribution, and utilization of known nutrients and the mechanisms responsible for an increased lifespan associated with dietary restriction. These investigations are done with physiologic, biochemical, and electronmicroscopic techniques. Other studies deal with comparative mammalian biochemistry including investigations of the stability of gene control mechanisms and the characterization of chromatin.

- Experimental Morphology Section—
  Dr. Richard C. Greulich

This section brings the most modern techniques of microscopy (TEM, SEM) and the related techniques of high resolution autoradiography and electron and X-ray probe microanalysis to bear on problems of structural-functional relationships during aging. Current interests include cell-cell interactions, junctional complexes, and epidermal aging.

Laboratory of Behavioral Sciences

- Psychophysiology Section—
  Dr. Bernard T. Engel

This laboratory is primarily concerned with the application of behavioral and psychological techniques and principles to the control or mediation of physiologic responses. There are both clinical research programs in the area of behavioral medicine and basic research programs using animal models to study neural control of cardiovascular function, as well as central neurotransmitter changes with age.

- Learning and Problem-Solving
  Section— Dr. David L. Arenberg

This section investigates the effects of aging on motor behavior, perceptual skills, learning, memory, and problem-solving ability. Laboratory facilities exist to measure cognitive and perceptual function in man, in addition to learning and motor behavior in rodents (including selected inbred strains of mice).

- Stress and Coping Section—
  Dr. Paul Costa

Investigators in this section examine personality and its influence on the aging individual's ability and efforts to adapt to problems of adult life. Research focuses on coping mechanisms that adults have developed to deal with such stresses as physical declines and illness, retirement, or widowhood. Longitudinal analysis is used to establish long-range predictors of coping success or failure.

Laboratory of Cellular and Molecular Biology—
Dr. Gunther L. Eichhorn

This laboratory conducts research basic to the aging process at the cellular and molecular levels, with emphasis on genetic information transfer. Highly qualified fellows have the opportunity to become familiar with the latest techniques for the solution of biological problems at the cellular and molecular level: NMR, CD, etc.

- Inorganic Biochemistry Section—
  Dr. Gunther L. Eichhorn

This section studies the effects of metal ions on nucleic acid structure and on genetic information transfer, including chromatin structure, RNA synthesis, and protein synthesis. It is primarily concerned with the mechanisms of introducing error into genetic information transfer. Studies are made of age changes in the structure of chromatin and ribosomes.

- Cellular Aging and Genetics Section—
  Dr. Gunther L. Eichhorn

Studies are carried out on the effect of metal ions on the viability of cells, and how they influence DNA synthesis and repair.

- Macromolecular Chemistry Section—
  Dr. Josef Pitha

Scientists in this section study the interaction of cells with synthetic macromolecules. Investigators probe age changes on the cell surface with specially designed macromolecules and also synthesize potential polymeric drugs.

Laboratory of Molecular Aging—
Dr. Bertram Sacktor

In this laboratory, highly qualified medical staff fellows have the opportunity to develop expertise qualifying them for careers in basic medical research. The thrust of the biochemical, biophysical, and physiologic programs are directed toward the biology of membranes, as it impacts on calcium and phosphorus homeostasis, salt/water balance, acid/base status, other ion and protein transport systems, and metabolic control mechanisms in various organs including the kidney, GI tract, bone, heart, and parotid gland. The problems and questions studied relate to: the molecular organization of the membrane; the mechanisms of vectorial ion and nonelectrolyte transport, the hormonal regulation of transport systems, the isolation of carriers and reconstruction of functional synthetic membranes, the turnover of membranes, and the failure to maintain membrane structure and function with age which leads to physiologic dysfunction and cell death.

Laboratory of Neurosciences—
Dr. Stanley I. Rapoport

This laboratory investigates the function, structure, physiology, biochemistry, and pharmacology of the central and peripheral nervous systems and of muscle, and the changes that take place during development and aging in animal models and in man.

- Section on Basic Neurosciences
  Dr. Stanley I. Rapoport

Scientists in this section study the ultrastructure, transport, and permeability at the blood-brain barrier, blood-ocular barriers, and peripheral nerves; experimental modifications of barrier permeability; regional cerebral metabolism and blood flow in relations to brain function; neuropharmacology in relation to stress, hypertension, and synaptic transmission; neurophysiology of nerve, muscle, and synapses; and factors regulating neuronal death and neuron-neuron and neuron-effector organ interaction and neuroendocrinology. The basic program is coordinated with the clinical research program on cerebral metabolism in aging and dementia.

National Institute of Allergy and Infectious Diseases

Richard M. Krause, M.D.,
Director
Kenneth W. Sell, M.D., Ph.D.,
Scientific Director
Michael M. Frank, M.D.,
Clinical Director

The National Institute of Allergy and Infectious Diseases (NIAID) annually appoints medical staff fellows for the laboratories described below. Fellows are selected by the clinical director, appointed to the Laboratory of Clinical Investigation, and begin after at least 1 year of residency training. Medical staff fellowship appointments in the other laboratories may begin after internship or residency training. In general, appointments to the Laboratory of Clinical Investigation carry responsibility for patients in the research program but are not otherwise different from those which begin after internship.

Specific answers to any questions or additional information may be obtained by applicants from the Scientific Director, NIAID, National Institutes of Health, Bethesda, MD 20205. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests and information desired.

Clinical Branch

Laboratory of Clinical Investigation—
Dr. Michael M. Frank
Laboratory of Immunoregulation—
Dr. Anthony S. Fauci

The NIAID appoints about 9 medical staff fellows. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned primary clinical responsibilities are made during the second or third year except as directed by the needs of the fellows' research.

There are 52 research beds. Medical staff fellows consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each fellow selects an area of investigative interest under the general preceptorship of the clinical director and the senior members of the staff of the Laboratory of Clinical Investigation or the Laboratory of Immunoregulation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in clinical investigation. Depending upon the area in which the medical staff fellow works, the subspecialty boards in infectious diseases or allergy-clinical immunology will usually credit the training received towards admission to these board examinations. Two to three staff fellows will be assigned to the Laboratory of Immunoregulation and six to seven to the Laboratory of Clinical Investigation.

Opportunities exist for research in a wide variety of areas of infectious, allergic, and immunological disease. Examples of studies now in progress are:

- The etiology, pathogenesis, and treatment of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases and vasculitis.
- Pathophysiology and treatment of autoimmune hemolytic anemia.
- Pathophysiology and treatment of hereditary angioedema.
- The pathophysiology and host defense response to bacteremia.

- Etiology and pathogenesis of the idiopathic hypereosinophilic syndrome.
- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- Mechanisms of regulations of immune reactivity in normals and in patients with immunologically mediated diseases.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The biochemical, neurophysiologic, and immunologic abnormalities of asthma and allergic diseases.
- The role of immune complexes in the production of disease.
- Immunopathologic mechanisms in parasitic infections.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Laboratory and clinical evaluation of antiviral substances.

Further information can be obtained if inquiries with specific questions are addressed to Dr. Kenneth W. Sell, Scientific Director.

Research Areas and Senior Staff
Allergic Diseases—
Michael A. Kaliner, M.D.,
Dean Metcalfe, M.D.
Bacterial Diseases—
John I. Gallin, M.D.
Clinical Immunology—
Michael M. Frank, M.D.,
Eric Brown, M.D.,
Keith Joiner, M.D.
Clinical Mycology—
John E. Bennett, M.D.
Clinical Parasitology—
Franklin A. Neva, M.D.,
Eric A. Ottesen, M.D.,
Theodore Nash, M.D.
Immunoregulation—
Anthony S. Fauci, M.D.
Medical Virology—
Stephen Straus, M.D.

Basic Research Laboratories

Laboratory of Viral Diseases—
Dr. Wallace P. Rowe

This group of scientists conducts research on the basic biology and ecology of chronic and persistent virus infections, with particular emphasis on oncogenic viruses.

This laboratory focuses on the biology of murine leukemia viruses. The genetics of transmission and expression of endogenous viral genomes, the biochemical nature of complete and incomplete endogenous viral genomes, and their role in tumorigenesis in the mouse constitute major areas of research.

These studies include investigations of the interactions between defective and competent viruses, the natural history and epidemiology of tumor viruses, genetic transmission of leukemia viruses in mice, and the viral and host genetic factors of importance in viral tumorigenesis.

Research Areas and Senior Staff
Leukemia Viruses—
Wallace P. Rowe, M.D.,
Janet W. Hartley, Ph.D.
Parvoviruses—
Malcom D. Hoggan, Sc.D.

Laboratory of Biology of Viruses—
Dr. Norman P. Salzman

The investigations in this laboratory are primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein, and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for medical staff fellows is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology, and medicine.

Research Areas and Senior Staff
Biochemical Virology—
Norman P. Salzman, Ph.D.
Macromolecular Biology—
Bernard Moss, M.D., Ph.D.
Molecular Structure—
James A. Rose, M.D.

Laboratory of Infectious Diseases—
Dr. Robert M. Chanock

This laboratory's activities are concerned with the basic behavior of viral and mycoplasmal pathogens that play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract and gastrointestinal tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as coronaviruses, acute gastroenteritis viruses, and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycoplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff
Epidemiology—
Albert Z. Kapikian, M.D.
Hepatitis Virus—
Robert H. Purcell, M.D.
Molecular Viral Biology—
Ching-Juh Lai, Ph.D.
Respiratory Viruses—
Robert M. Chanock, M.D.

Laboratory of Immunogenetics—
Dr. Thomas J. Kindt

This group is involved in basic research on major gene complexes involved in immune function. The approaches used in these studies emphasize structural, serologic, and genetic investigations. The techniques used include quantitative radioimmunoassays, protein structure determinations, recombinant DNA technologies including gene cloning and nucleotide sequencing, preparation and study of T- and B-cell hybridomas, and a variety of immunologic assays for cellular and humoral components of the immune response.

Areas of active investigation include: studies on cloning, sequencing, and genetic analyses of genes for rabbit immunoglobulins and MHC products; structural and functional studies on murine H-2 antigens and human HLA antigens with emphasis on the D/DR complex; regulation of immunoglobulin gene expression during maturation of lymphocytes; use of hybridoma antibodies to investigate components of lymphoid cell membranes; and evaluation of the role of the MHC in the control of responses to individual antigens or infectious agents.

The opportunity is available for medical staff fellows to study in any of these areas under the preceptorship of a senior laboratory member. During their tenure, appointees become proficient in modern techniques of structural biochemistry and molecular biology and in quantitative and qualitative immunologic procedures. In addition, they gain an understanding of the genetic mechanisms underlying the ability to mount an immune response.

Research Areas and Senior Staff

Immunoglobulin Genetics—
T. K. Kindt, Ph.D.,
J. A. Sogn, Ph.D.
Membrane Antigens—
J. E. Coligan, Ph.D.
Immunobiology—
K. W. Sell, M.D., Ph.D.
Molecular Immunogenetics—
E. E. Max, M.D., Ph.D.
Human Histocompatibility—
J. A. Sachs, M.D., Ph.D.

Laboratory of Immunology—
Dr. William E. Paul

This laboratory is engaged in the study of various aspects of cellular immunology, immunogenetics, and immunochemistry, particularly as they bear on a fuller understanding of the biological significance of the immune response and on the role of immune mechanisms in the prevention and pathogenesis of human disease.

Areas of active investigation include the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic and idiotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells. Studies of the role of different lymphocyte classes in many human diseases are under way, and models for the study of cellular immune responses in tumor immunity are being developed. Utilization of many modern techniques in the study of immune responses will be made, including production and use of monoclonal antibodies, cloning and long-term growth of B- and T-lymphocyte lines, and molecular genetic analysis of cells of the immune system. Medical staff fellows will have the opportunity to participate in studies in one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff

Cellular Immunology and Genetic Regulation of the Immune Response—
Ira Green, M.D.,
William E. Paul, M.D.,
Ronald H. Schwartz, M.D., Ph.D.,
Ethan H. Shevach, M.D.
Molecular Immunology and Immunogenetics—
Mark Davis, Ph.D.,
Rose G. Mage, Ph.D.

Laboratory of Microbial Immunity—
Dr. Richard Asofsky

The laboratory is primarily concerned with the elucidation of basic mechanisms involved in both the cellular and humoral immune responses to microbial and tissue antigens.

Several major areas of investigation, each employing a wide variety of immunologic methods, offer the medical staff fellows comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. The significance of interaction among different kinds of lymphoid cells in the induction and manifestation of immunity is being studied in graft-versus-host reactions and in humoral immune responses. The development, distribution, and susceptibility of the interacting components to various treatments that suppress or amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations.

Autoimmune phenomena are studied using immune complex nephritis and autoimmune encephalomyelitis as models. Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. The relationship of this disease to the presence and activity of such integrated viruses as the murine leukemia agents are studied. The nature of the immune response to protozoal parasites, including the antigenic and genetic requirements for the expression of this immunity, are studied. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

Research Areas and Senior Staff
Experimental Pathology—
Richard Asofsky, M.D.
Microbiology and Immunology—
Phillip J. Baker, Ph.D.
Virology and Cellular Immunology—
Herbert C. Morse III, M.D.
Experimental Autoimmunity—
Sanford H. Stone, Ph.D.

Laboratory of Parasitic Diseases—
Dr. Franklin A. Neva

This group of scientists is engaged in both basic and applied studies of parasitic diseases, with emphasis on those affecting man. A variety of protozoan (malaria, trypanosomes, giardia, leishmania, amebae, and toxoplasma) and helminth (schistosomes, filaria, and strongyloides) parasites are used for experimental work. Current studies include comparative mechanisms of energy transfer, ultrastructure of parasites, and host-parasite interactions *in vitro* and *in vivo*.

Increasing emphasis is being devoted to the immunologic response of the host in parasitic infections, both humoral and cellular. Another area of emphasis concerns the biochemical and immunologic characteristics of parasite surfaces and their interactions with the host cell membrane. Some experimental infections such as leishmaniasis, amebiasis, schistosomiasis, and filiarisis in animals are used as models of naturally occurring disease in man. The availability of different species of human as well as simian malaria parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate, certain problems that can only be investigated in the field are studied in collaboration with institutions overseas. Clinical investigators from the Laboratory of Parasitic Diseases are associated with the Laboratory of Clinical Investigation within the Section of Clinical Parasitology. Thus, selected patients are seen and studied as inpatients or outpatients at the Clinical Center.

Within limits of space and available guidance by a member of the senior staff, medical staff fellows can select their area of work and a preceptor. In addition, an organized program provides medical staff fellows with an exposure to clinical parasitology.

Research Areas and Senior Staff

Host-Parasite Relations—
A. W. Cheever, M.D.
Cell Biology and Immunology—
F. A. Sher, Ph.D.
Clinical Parasitology—
F. A. Neva, M.D.,
T. E. Nash, M.D., and
E. A. Ottesen, M.D.
Malaria—L. H. Miller, M.D.
Parasite Growth and Differentiation—
L. S. Diamond, Ph.D.
Physiology and Biochemistry—
E. C. Weinbach, Ph.D.

Laboratory of Molecular Microbiology—
Dr. Malcolm A. Martin

This laboratory uses molecular biological techniques to study microorganisms and their capacity to produce disease in vertebrate hosts. Of prime importance is the biochemical characterization of viral, bacterial, and plasmid genomes and the detailed analysis of DNA segments that regulate the expression of specific gene products.

Programs involving DNA and RNA tumor viruses focus on those portions of the viral genome that encode proteins that initiate and/or maintain the transformed state. The roles of the host cell genetic apparatus and the immunologic system in augmenting the effect(s) of specific viral gene products during oncogenesis are also investigated. Other programs investigate the process of bacterial transformation with special emphasis on the role of plasmids in transferring genetic information from one organism to another.

Biochemical and biophysical techniques, such as molecular cloning, nucleic acid hybridization, and DNA sequencing, are used in combination with procedures such as monoclonal antibody production and immunoprecipitation to answer basic questions involving the structure and function of prokaryotic and eukaryotic genes.

Research Areas and Senior Staff
Biochemical Virology—
Malcolm A. Martin, M.D.,
Mark A. Israel, M.D.,
Yoshiaki Ito, M.D., Ph.D.
Viral Biology—
Kenneth Takemoto, Ph.D.
Andrew Lewis, M.D.
Bacterial Virulence—
Donald LeBlanc, Ph.D.
Mycoplasma—
Joseph G. Tully, Ph.D.

Rocky Mountain Laboratories— The Rocky Mountain Laboratories, located at Hamilton, Montana, consist of the following:

Laboratory of Persistent Viral Diseases—Dr. Bruce W. Chesebro

This group is concerned with studies of virus-host interaction with the primary aim of elucidating mechanisms involved in establishment, maintenance, and elimination of persistent viral infections. Investigations are also made on involvement of persistent virus infection and autoimmune and immune complex diseases. Appropriate models being examined include rabies virus, scrapie, murine leukemia viruses, and Aleutian disease virus of mink.

Research Areas and Senior Staff
Murine Leukemia Viruses—
Bruce Chesebro, M.D.,
John Portis, M.D.,
Miles Cloyd, Ph.D.,
and Leonard Evans, Ph.D.
Aleutian Disease Virus—
Marshall Bloom, M.D.
Scrapie—
Richard Race, D.V.M.
Rabies—
Donald Lodmell, Ph.D.
Immunology—
John Coe, M.D.

Laboratory of Microbial Structure and Function—Dr. John Swanson

Bacteria pathogenic for man are the major topics for study in this laboratory. Special attention is paid to surface components of selected bacteria, rickettsiae, mycoplasmas, and chlamydiae that relate to the virulence and/or pathogenicity of these organisms. In addition to biochemical and immunochemical studies of these organisms' surface constituents, current studies also include investigation of the metabolic capabilities and characteristics of selected rickettsial agents, toxin and other products of staphylococci and *Bordetella pertussis,* and genetic control or expression of these bacterial elements. The general goal of these studies is to document, characterize, and understand interactions between pathogenic prokaryotes and cellular or humoral components of the infected host so mechanisms of pathogenicity and virulence can be elucidated.

Research Areas and Senior Staff—
Borrelia—
Alan Barbour, M.D.
Chlamydia—Harlan Caldwell, Ph.D.
Endotoxic and Adjuvant Components of Bacteria—
Charles McLaughlin, D.V.M., Ph.D.
Gonococci—
John Swanson, M.D.,
Leonard Mayer, Ph.D.

Pertussis—
Mark Peppler, Ph.D.
Rickettsiae—
Jim Williams, Ph.D.

Epidemiology Branch—
Dr. Robert Philip

The staff of this branch plans and conducts epidemiologic investigations and studies on natural histories of human diseases. The senior staff provides consultative services on biometric analysis and epidemiologic methods to other investigators and provides seroepidemiologic and diagnostic support for the branch and selected collaborative projects outside of the branch. One research group performs surveillance of arthropod-borne agents of human disease importance. Another group undertakes detailed histopathologic investigations of naturally occurring diseases in animals, naturally occurring slow viral diseases of animals, and infectious problems in animal models which may be related to findings in counterpart diseases of man.

Research Areas and Senior Staff
Epidemiology—
Dr. Robert Philip, Ph.D.
and Elisabeth A. Casper
Arthropod-borne Diseases—
Willy Burgdorfer, Ph.D.,
Carleton M. Clifford, Ph.D.,
Conrad Yunker, Ph.D., and
James Keirans, Ph.D.
Histopathology—
William Hadlow, D.V.M.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Lester B. Salans, M.D.,
Acting Director
J. E. Rall, M.D., Ph.D.,
Director of Intramural Research
Phillip Gorden, M.D.,
Clinical Director

Appointments in Clinical Research

Each medical staff fellow is assigned to one of the Institute's clinical branches or sections, within which he or she carries out both clinical work and laboratory studies. The fellow is, in effect, an apprentice investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The fellow is encouraged to choose his or her own problem for independent investigation, if facilities required for its successful pursuit and if technical advice and supervision necessary are available. In addition, the fellow provides professional care for research patients admitted to the service of the branch chief and assists in the outpatient department. There is considerable variation among the branches of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) with respect to the proportion of the fellow's time required for patient care activities.

Medical staff fellows of the Clinical Endocrinology, Diabetes, and Metabolic Disease branches participate in a 3-year Interinstitute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIADDK fellows may spend a third year in the Endocrinology Program.

The Institute recruits about 10 new medical staff fellows each year. The assignments are for 2 or 3 years and usually are not extended. One year of internship and at least one year of residency should generally be completed before the appointment begins.

Vacancies do not necessarily occur within each program each year; the Program Area Selection Checklist indicates the positions to be filled. The chiefs of branches or sections with openings and the clinical director screen applications and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical research branches are listed below with the names of the permanent investigators and a brief sketch of the areas of interest. Prospective applicants desiring more information should write to Dr. Phillip Gorden, Clinical Director, NIADDK, Building 10, Room 9N222, NIH, Bethesda, MD 20205. Supplementary information sheets on each branch, together with selected bibliographic citations' are available on request.

Appointments in Laboratory Research

NIADDK has four positions in laboratory research available each year for medical staff fellows. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During their stay here, fellows will devote the larger part of their time to laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should candidates elect a clinical area, they would not participate in clinical care of patients. The medical staff fellow, approximately 1 year prior to beginning, will visit NIADDK to select the laboratory and preceptor with whom he or she wishes to work. Candidates desiring further information about the laboratories, staffs, and bibliography can obtain this by writing Dr. J. E. Rall, Director of Intramural Research, NIADDK, National Institutes of Health, Bethesda, MD 20205.

Medical Staff Fellows in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment for studying the epidemiology of chronic disease such as diabetes, arthritis, and cholelithiasis among the Pima Indians of Arizona. In addition, clinical research opportunities in the causes, complications, and treatment of diabetes are available at the Phoenix Clinical Research Section in the Phoenix Indian Medical Center. Candidates occasionally begin this fellowship upon completion of an internship but, in most cases, most postdoctoral training has been completed. Candidates interested in clinical research are encouraged to write to Dr. Stephen L. Aronoff, Phoenix Clinical Research Section, 4212 N. 16th Street, Phoenix, Arizona 85016. Those interested in epidemiology should write Dr. Peter H. Bennett, Epidemiology and Field Studies Branch, NIADDK, 1440 E. Indian School Road, Phoenix, AZ 85014, for more detailed information.

Clinical Research Branches

Arthritis and Rheumatism Branch—
Dr. John L. Decker

- Section on Connective Tissue Disease—Drs. John L. Decker, James E. Balow, John H. Klippel, Paul H. Plotz, Alfred D. Steinberg, and Ronald L. Wilder

The pathogenesis of systemic lupus erythematosus (human and mouse models) is under study. Suppressor and activator lymphocyte isolation, development of stable immune complexes, and studies of reticuloendothelial function are in progress. Clinical work is on cytotoxic drugs in lupus nephritis, on survivorship variations with disease pattern, and on effects of drugs on patients with lupus or rheumatoid arthritis. Cytopheretic and plasmapheretic techniques are being studied in patients with connective tissue disease.

- Section on Chemical Immunology—
  Dr. Henry Metzger

The section is involved in fundamental research on the structure and mechanism of immunoglobulins and their receptors on cells, using protein chemistry, immunochemistry, tissue culture, and electron microscopy techniques.

Clinical Endocrinology Branch—
Drs. Jacob Robbins, Jan Wolff,
Saul Rosen, Harold Edelhoch, and
Bruce Weintraub

Activities in this branch range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid and polypeptide hormones. Laboratory research includes fundamental and applied protein chemistry, including studies on hormone transport proteins and polypeptide hormones, the mechanism of hormone actions, control mechanisms in secretory cells, adenylate cyclase-receptor interactions and membrane biochemistry, and the biosynthesis of polypeptide hormones.

Clinical Hematology Branch—
Dr. N. Raphael Shulman

Laboratory work concerns the biochemistry of blood coagulation, platelet physiology and metabolism, and various problems in the field of immunohematology. Interests currently include isolation and characterization of antihemophilic factors, correlation of platelet metabolism with function involving analyses of membrane reactions and secretory phenomena, and studies of immunologic mechanisms of platelet injury, including drug- and allo-immune problems. Clinical work involves patients with hemorrhagic and immunologic disorders relevant to the laboratory studies.

- Section on Cell Biology and
  Biochemistry—Dr. Harvey B. Pollard

The primary interest of this group is in mechanisms of secretion of proteins, hormones, and transmitters from neuroendocrine and other cells. Problems under investigation currently include how secretory and other organelles move around in cells, how calcium acts to fuse secretory vesicles to plasma membranes, and how release of vesicle contents during exocytosis subsequently occurs. Special interest is placed on proteins such as synexin that may mediate such events, on the relation of cytoskeletal elements such as actin to secretory functions, and on ion transport sites in vesicle and plasma membranes that may be important in regulating secretion.

Diabetes Branch—
Drs. Jesse Roth and Phillip Gorden

Focus is on peptide hormones, especially insulin, growth hormone, and insulin-like growth factors. Recent work has been largely on the interaction of the peptide hormones with their receptors on the surface membrane of target cells. The emphasis is on diseases where the concentration or affinity of the receptor changes in response to intracellular or extracellular events. A broad range of experimental approaches is used to explore these processes including cell culture, purification of hormones and of membrane components, and studies of rodents and people with a wide variety of insulin-resistant conditions.

Digestive Diseases Branch—

- Section on Gastroenterology—
  Drs. Jerry D. Gardner and
  Robert T. Jensen

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive, and immunologic processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology, biochemistry, and immunology.

- Liver Diseases Section—
  Drs. E. Anthony Jones and
  Jay H. Hoofnagle

Programs are concerned with research into hepatic physiology, immunology, and disease. Laboratory research projects include studies of cellular immunology and the modulation of immune responses in primary biliary cirrhosis and other chronic liver diseases; investigations of the significance of various viral antigens and antibodies in chronic type B hepatitis; characterization of cell-surface receptors on isolated hepatocytes, Kupffer cells, and hepatic endothelial cells; and the evaluation of the pathogenetic mechanisms that mediate the encephalopathy in an animal model of fulminant hepatic failure. Clinical investigations include studies of the natural history of chronic type B hepatitis and chronic non-A, non-B hepatitis, evaluations of the efficacy of antiviral agents in the treatment of chronic type B hepatitis, and a controlled trial of immunosuppressive therapy in primary biliary cirrhosis.

Genetics and Biochemistry Branch—
Drs. Elizabeth F. Neufeld,
R. Daniel Camerini-Otero,
and Michael A. Zasloff

The branch conducts studies in biochemical and molecular genetics which range from the very basic (eukaryotic gene isolation and organization, the control of gene expression, gene transfer, and the biochemical basis of lysosomal storage disorders) to the highly applied (development of new diagnostic tests and carrier detection for a number of genetic diseases). The branch participates in the NIH Interinstitute Clinical Genetics Program. Clinical investigations include studies on patients with fibrodysplasia ossificans progressiva, a heritable disorder characterized by the accumulation of heterotopic bone in soft tissues, and clinical trials of several novel drugs are under way. Studies are also being conducted on the heterogeneity of Marfan-like diseases, such as contractural arachnodactyly.

Metabolic Diseases Branch—
Drs. Gerald D. Aurbach,
Stephen E. Marx, and
Allen M. Spiegel

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, parathyroid hormone, and calcitonin. The clinical program involves studies of patients with disorders of mineral metabolism. These include patients with hereditary resistance to parathyroid hormone or to calciferols. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is available for *in vitro* studies on control of hormone secretion.

Pediatric Metabolism Branch—
Paul A. di Sant'Agnese

Cystic fibrosis of the pancreas is the target of both laboratory and clinical work. Glycoproteins, polyamines, the circulating "cystic fibrosis" factors, and other substances are analyzed for their possible relationship to the pulmonary, pancreatic, and sweat gland involvement, as well as other facets of this genetic disease. Techniques used include tissue culture, amino acid analyses, automated ion exchange and thin-layer chromatography, radioisotope analyses by liquid scintillation counting, and tissue culture. A variety of clinical aspects such as vitamin E deficiency, the renin-aldosterone axis, and cyclic nucleotides are studied, and the course and complications of cystic fibrosis are documented.

Phoenix Clinical Research Section—
Drs. Stephen L. Aronoff,
Barbara V. Howard, Lester B. Salans,
and Peter H. Bennett

This section is currently involved in studies of diseases particularly prevalent among southwestern American Indians. One of the major areas under investigation is diabetes mellitus in the Pima Indian population. This group has the world's highest reported prevalence of type II (noninsulin dependent) diabetes. The geographical proximity of this unique population to the Phoenix area provides an excellent opportunity for insight into the causes and complications of type II diabetes. A problem closely related to the diabetes in this group is that of obesity. These areas are under intensive scientific investigation in both the 24-bed clinical research unit and the basic science research laboratory which are colocated within the Indian Health Service Referral Hospital, Phoenix, Arizona.

Clinical studies currently in progress include whole-body insulin resistance, solid and liquid gastric emptying, nutrition-induced alterations in metabolism, lipid and lipoprotein metabolism, and dietary and exercise therapy in the treatment of diabetic patients. The laboratory research is centered around insulin receptor studies, insulin-mediated glucose metabolism in diploid fibroblasts from diabetic and nondiabetic donors, fat cell metabolism, rat pancreatic islet perfusion studies, as well as a variety of studies supporting the clinical investigations.

Close collaboration with the Epidemiology and Field Studies Section allows investigation into the prevalence of not only diabetes and obesity, but also cardiovascular disease, gallbladder disease, lipid and lipoprotein abnormalities, and rheumatoid arthritis in the Pima Indians.

Basic Research Laboratories

Laboratory of Biochemical Pharmacology—Drs. Herbert Tabor, Simon Black, Victor Ginsburg, Leonard D. Kohn, and Kolomon Laki

The work of this laboratory includes a large variety of biochemical and physiologic investigations. Included are studies on polyamine synthesis and action, nucleic acid and protein biosynthesis, tryptophan biosynthesis, the structure of cellular membranes, and yeast and *Escherichia coli* genetics. Studies are also carried out on developmental biology and organ regeneration in the rat, and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

One section is concerned in particular with the structure, function, and bioenergetics of biological membranes and the mechanism by which various effectors—hormones, toxins, neurotransmitters, interferon, and viruses—transmit their information through these membranes to the interior of the cell. Another subsection studies diverse aspects of the related hormones insulin and somatomedin, including: structure, biosynthesis, mechanism of action, biological role, and genetic syndromes of hormone resistance. A third section is particularly concerned with the biology of the complex carbohydrates of animal cell surfaces.

Laboratory of Biochemistry and Metabolism—
Drs. G. Gilbert Ashwell,
William B. Jakoby, and
Yale J. Topper

The laboratory program is directed toward an understanding of the basic biochemical mechanisms involved in both normal and abnormal biological processes. Within this general framework, independent projects cover a broad range of biochemical investigations.

A brief summary of the major areas under study includes an examination of the hormone-dependent differentiation and development of mammary gland tissue in normal and hypophysectomized rats; a detailed study of growth and development whereby the formation of the primary septum of yeast is used as a molecular model for morphogenesis; the isolation and characterization of specific hepatic receptors that regulate the metabolism of serum glycoproteins; and a study of the cluster of enzymatic activities classified as enzymes of detoxication that function in the conjugation of foreign compounds in mammals and the role of cellular factors involved in the biosynthesis and differentiation of lymphocytes in spleen and thymus. In addition to the above general areas, specific projects of individual investigators include a study of the particulate enzymes involved in carbohydrate metabolism, identification of sulfur-containing nucleotides in tRNA, biochemical abnormalities in human cystinosis, genetic control of bacterial membrane proteins, and thermodynamic and kinetic studies on enzymatic mechanisms.

Laboratory of Bioorganic Chemistry—
Drs. John W. Daly and
Donald M. Jerina

This laboratory's research mission is to elucidate the mechanism of interaction of pharmacologically active substances with biological systems. Research is designed toward the development of new chemical agents as tools for the study of membrane and cytosol functions of cells. New mechanisms of action or metabolism of such agents are also investigated for their potential use as therapeutics. Development and application of modern techniques of organic chemistry for the synthesis, separation, and spectral investigation of these chemical agents and their interactions with macromolecules are emphasized. The goal is to provide insights into the normal and pathologic function of biological systems and to delineate the metabolic formation, fate, and action of physiologically active agents such as amino acids, biogenic amines, cyclic nucleotides, hormones, neurotransmitters, and steroids. Studies include pharmacologically active agents such as natural products, therapeutic agents, toxins, carcinogens, and mutagens.

Laboratory of Chemical Biology—
Drs. Alan N. Schechter and Hiroshi Taniuchi

Research in this laboratory is concerned with the three-dimensional structure of proteins and the relationships between structure and function. One set of studies being carried out by Dr. Taniuchi, and by Dr. Chaiken, involves the interaction between fragments derived from particular proteins that have the capacity to interact noncovalently with the regeneration of native structure and function. A second model system concerns sickle cell hemoglobin and fetal hemoglobin. In this work, by Dr. Schechter and his group, attempts are being made to understand the nature of abnormal physical and physiologic properties in terms of structure, to develop means for detecting small amounts of such abnormal molecules in the biological material, and, in the case of sickle cell hemoglobin, to test the capacity of various amino acids and small peptides to correct the structural and functional lesion. Another group is currently involved with the isolation and characterization of human interferon and hopes eventually to determine the structure of this substance and synthesize it. Finally, Dr. Steers and his colleagues are investigating membrane properties using the paramecium as the test object.

Laboratory of Chemical Physics—
Drs. Edwin D. Becker, Elliot Charney, William A. Hagins, William A. Eaton, and Ira W. Levin

Research in this laboratory is characterized by the application of sophisticated physical techniques to the solution of a wide range of problems. Among the current research interests of the staff are: analysis of the kinetics and mechanism of aggregation of hemoglobin-S, study of the association of mononucleotides and of the conformational behavior of polynucleotides, investigations of the excitation of visual photoreceptors and resultant ionic processes in membranes, analysis of excited electronic states of small molecules in the vapor phase and in molecular beams, development of methods for asymmetric synthesis, study of the structural characteristics of model membrane systems, and the structure and dynamic behavior of nucleic acids and nucleoproteins. Much of the research involves the use of a variety of spectroscopic methods—for example, nuclear and electron magnetic resonance, laser-Raman and resonance Raman spectroscopy, electric-field-induced dichroism, and ultraviolet and visible microspectrophotometry.

Laboratory of Chemistry—
Drs. Bernhard Witkop, L. A. Cohen, A. Brossi, C. P. J. Glaudemans, and D. Johnson

In the oldest laboratory of the Institute (founded June 20, 1905), chemistry is represented in its broadest context in five independent sections investigating the mechanisms of enzymatic reactions and their simulation, medicinal chemistry, immunochemistry, novel toxins, metabolism, antiviral agents, interferon, and analysis and instrumentation. Some of the recent achievements concern the role of retinoids in bladder cancer, effects of novel colchicine derivatives on microtubules, separation of addictive from analgesic properties in new synthetic morphine substitutes, characterization of sodium channels in electrogenic membranes by a frog toxin, the acetylcholine receptor, development of fluorinated amino acids and biogenic amines as selective probes and inhibitors of enzymatic and metabolic processes, hypoxic cells sensitizers, cytotoxic agents selective for cancer cells, the interaction between antigens and monoclonal antibodies, recombinant hybrid immunoglobulins and the detailed structure of fungal antigens, and chemistry and biochemistry of interferon induction and interferon-related enzymes.

Laboratory of Experimental Pathology—
Drs. Robert M. Friedman, Ned Feder,
J. H. Tjio, and Lois Tice

The laboratory carries out basic studies broadly relating to the pathogenesis of various disease states. Typical of research projects now under investigation are: molecular biology of the transcription of a viral genome, mechanism of action of interferon, cytogenetics and immunology, pathogenesis of amyloidosis, genetics and neurobiology, and ultrastructural analysis of cellular function. Techniques used include gel electrophoresis, chromatographic procedures, ultracentrifuge analysis and separation, conventional histopathology and electron microscopy, tissue culture, viral assays, cytogenetics, and freeze-etching electron microscopy.

Laboratory of Molecular Biology—
Drs. Martin Gellert, Jun-ichi Tomizawa,
Gary Felsenfeld, David R. Davies,
Robert Martin, H. Todd Miles,
and Terrell Hill

The work of the laboratory is concerned with understanding biological processes in terms of structure and reaction at the molecular level. Research includes direct investigations of biological processes, such as genetic recombination, DNA replication, and protein synthesis, studies of the mechanism of transformation by SV40 (a virus causing tumors in hamsters), and studies of the mechanism of hemoglobin S gelation, the phenomenon that causes sickling of red blood cells in sickle cell anemia. Other investigations are concerned with the structure and chemical properties of biologically important materials. These include studies of the organization of DNA and proteins in chromatin, investigations of protein structure by X-ray diffraction and of nucleic acid and polynucleotide structure by diffraction and spectroscopic methods, and theoretical studies of the mechanisms of free energy transduction, muscle contraction, membrane properties, and biochemical kinetics.

Laboratory of Nutrition and Endocrinology—
Drs. Robert T. Simpson,
Martin Rodbell, John G. Bieri,
Bernard T. Kaufman, and
Robert O. Scow

This laboratory consists of five sections devoted to various biochemical and physiological investigations. The Section on Nutrition carries out studies on the role of tocopherols in cellular oxidative processes and on the intermediary metabolism of lipids, carbohydrates, and amino acids in the small intestine. The Section on Endocrinology investigates hormonal regulation of enzymes involved in chylomicron uptake and metabolism in adipose and mammary tissue, the influence of hormones on cellular development and metabolism, and the disposition of fat and metabolites in the cell as viewed from ultrastructural studies. The Section on Vitamin Metabolism investigates the structural and functional aspects of dihydrofolic reductase and other enzymes involved in folic acid metabolism. The Section on Membrane Regulation studies the mechanism of action of hormones on adenylate cyclase and other membrane regulatory processes. The Section on Developmental Biochemistry investigates the structure and function of chromatin and the regulation of gene function during development.

Laboratory of Physical Biology—
Drs. R. J. Podolsky and J. Buck

This laboratory carries out a broad range of studies. The mechanism of muscle contraction is studied in intact cells and in simplified preparations, using time-resolved X-ray diffraction in conjunction with mechanochemical techniques. Activation of muscle cells is examined by measuring calcium movement between the myofilaments and the sarcoplasmic reticulum in skinned muscle fibers. Lipid dispersions in water are investigated as models of the structure and physical states of lipids in cell membranes. The actions of ionizing radiation on macromolecules are used to determine the *in vivo* size of the functional units for different biological activities (hormone receptors, enzyme complexes, and regulatory units). Other subjects under investigation are enzyme organization in unicellular organisms, metamorphosis in insects, human red cell sickling, and biological rhythms and entrainment.

Mathematical Research Branch—
Dr. John Z. Hearon

The branch conducts research on the mathematical and theoretical aspects of biological problems and the development of analytical and numerical methodology underlying such an approach. The research programs are designed to provide a formal basis and theoretical apparatus for the rational analysis and quantitative interpretation of biological phenomena. *Research is organized around biological subject-matter areas rather than around subdisciplines of mathematics.* Major research topics include transport and consumption of substrates at the tissue-capillary level, electrotonus in dendritic systems, neuroelectric signaling, bifurcation and stability studies with special reference to propagation of nerve impulse and diffusion-reaction systems, kinetics and thermodynamics of metabolic systems, problems in linear algebra arising from linear kinetics of physiological systems, and mathematical modeling of renal functions.

National Institute of Child Health and Human Development

Betty H. Pickett, Ph.D.,
Acting Director
James B. Sidbury, M.D.,
Scientific Director,
Acting Clinical Director

Appointments in Clinical Research

The National Institute of Child Health and Human Development offers eight medical staff fellowship positions in clinical research each year. Appointments are for 2 or 3 years, depending on the program chosen.

The Endocrinology and Reproduction Research Program selects two or three medical staff fellows yearly. Applicants should be Board eligible in internal medicine or obstetrics and gynecology prior to the initiation of the fellowship. Internists participate in the Combined Endocrinology Training Program of the NIH, which leads to Board eligibility in the subspecialty of endocrinology and metabolism. Medical staff fellows in obstetrics and gynecology participate in a combined gynecology-endocrinology fellowship with the NIH, Walter Reed Army Hospital, and National Naval Medical Center, which leads to Board eligibility in gynecologic endocrinology. Appointments are generally made 2 years in advance of the starting date of the fellowship.

For the Pediatric Medical Program, applicants should preferably have completed PL-3 level training by the time of entry. Earlier entry will also be considered. The components of the program include endocrinology, nutrition, metabolism, biochemical genetics, and developmental gastroenterology. The first year includes ward responsibilities.

In both the Endocrine and Pediatric Programs, the medical staff fellow will identify the preceptor and laboratory in which he or she will do research during the first 2 months. The fellow may elect to work in any of the laboratories of the NICHD Intramural Research Program.

Appointments in Laboratory Research

Medical staff fellows may work in one of the basic science laboratories.

Clinical Research Branches

Neonatal and Pediatric Medicine Branch—
Dr. J. B. Sidbury

Research is conducted in diagnosis, treatment, and mechanisms of diseases of infants and children. Emphasized are basic nutritional studies, lung biochemistry, endocrinology, and inborn errors of metabolism. The fellows may participate in the clinical program of the Interinstitute Genetics Program and work in genetics in the laboratory of his or her choice. The program qualifies the candidate for Board certification. Similarly, pediatric endocrinology is a part of the Interinstitute Endocrine Program; clinical participation is required to qualify for Board certification.

- Section on Human Biochemical and Developmental Genetics—
  Dr. Joseph D. Schulman

Various inborn errors of metabolism, especially disorders affecting the sulfur amino acids, are investigated. Metabolism and transport of the amino acids is an area of investigation as well as the long-chain fatty acids in relation to adrenal leukodystrophy.

Developmental Endocrinology Branch—
Dr. Lynn Loriaux

The endocrine concomitants of growth, development, and differentiation are examined. Current laboratory investigations include studies of the mechanism and control of steroid biosynthesis, secretion, transport, and target tissue action. Of particular clinical interest are disorders of adrenal function, male and female infertility, and disorders of puberty and secondary sexual development.

Two medical staff fellows are accepted each year. During the first year, the fellow rotates among the endocrinology branches of the NIH to gain a broad knowledge of clinical endocrinology. The next 2 years are spent primarily in laboratory investigation in collaboration with a senior investigator in any laboratory of the Institute.

Pregnancy Research Branch—
Dr. Gary D. Hodgen

Interests of this branch range from the physiology of pregnancy, the identification of genetic and developmental factors which contribute to perinatal fetal and maternal morbidity and mortality, through fertility regulation and toxicologic aspects of ovarian function to fertilization and implantation. These studies employ a variety of animal models, as well as laboratory aspects of clinical investigation. Fellows in obstetrics and gynecology selected for the national fellowship in reproductive medicine will rotate among gynecologic and obstetrical endocrinology programs at NIH, Walter Reed Army Hospital, and the National Naval Medical Center during the first year. The next 2 years are spent primarily in laboratory investigation in collaboration with a senior investigator.

- Section on Endocrinology—
  Dr. Gary D. Hodgen

Basic research is conducted in reproductive endocrinology and in laboratory aspects of clinical investigation. Major emphasis is placed on nonhuman primates for studies of ovarian function and pregnancy and on the physiology and chemistry of gonadotropins.

Endocrinology and Reproduction Research Branch—
Dr. Kevin J. Catt

This branch conducts an integrated program of clinical, biochemical, and biologic studies pertinent to endocrinology and reproductive biology.

- Section on Hormonal Regulation—
  Dr. Kevin J. Catt

Emphasis is placed on the receptor binding and actions of polypeptide hormones such as GnRH, gonadotropins, and angiotensin. Major concerns include the characterization and isolation of membrane receptors and analysis of the receptor-second messenger systems in target cells of peptide hormones.

- Section on Molecular Endocrinology—Dr. Maria Dufau

This group investigates the molecular basis of peptide hormone action, with particular emphasis on the control of gonadal and adrenal function; analyzes the nature of gonadotropin receptors and activation of steroid biosynthesis in testis and ovary; and investigates the properties and biological activity of circulating gonadotropins in physiologic regulation and clinical disorders of pituitary and gonadal function.

- Section on Biophysical Endocrinology—Dr. David Rodbard

This section performs mathematical and statistical analysis of endocrine regulatory processes and the physical properties of protein hormones studied by polyacrylamide gel electrophoresis; applies mathematical modeling, computer simulation, and biophysical methods to studies on hormone-receptor interaction and regulation of the ovarian cycle; and investigates cardiovascular changes in thyroid disease.

Child and Family Research Branch—
Dr. Leon J. Yarrow

Research in this branch has concentrated on cognitive, social, and motivational development and on early parent-infant interaction. Current investigations are concerned with methodologic and theoretic issues regarding early environmental influences, reciprocal interactions between the child and environment, the assessment of neonatal characteristics, and early temperament and the development of measures for assessing mastery motivation during infancy. Studies are also being conducted on the psychological effects of cesarean delivery on mother's and father's interactions with their infants and the effects of varying patterns of maternal employment on family interaction. Studies are being planned on the development of children with endocrine disorders.

Research Laboratories

Laboratory of Developmental Neurobiology—
Dr. Philip G. Nelson

The neurobiologic basis for short- and long-term interaction between nerve cells is studied electrophysiologically and biochemically. The central neural mechanism underlying sensory discrimination in primates is studied by electrophysiologic and behavioral techniques. Combined molecular and behavioral methods are used in the analysis of experiential modifications of brain function.

- Section on Brain and Behavior—Dr. David Symmes

Electrophysiologic correlates of sensory coding and discriminative behavior are analyzed with microelectrode computer techniques. The focus of interest is in vocal communication among subhuman primates and its possible relationships to human speech.

- Section on Functional Neurochemistry—Dr. Harold Gainer

Emphasis is on the analysis of biochemical changes in identified neurons associated with electrophysiologic and behavioral alterations. Specific neuronal protein synthesis and axoplasmic transport, glial-neuronal interactions, pacemaker activity, and neural peptides are studied.

- Section on Intermediary Metabolism—Dr. Gordon Guroff

This section is studying the mechanism of action of enzymes of neurochemical interest, the biosynthesis and degradation of macromolecules in neural tissue, and the mechanism of action of nerve growth factor. Other studies concern the evaluation of the effects of excesses or deficiencies of intermediary metabolites on cellular differentiation.

- Section on Neurobiology—Dr. Phillip G. Nelson

Tissue-cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied electrophysiologically and biochemically. Long-term interactions between neurons and between nerve and muscle are of particular interest.

- Section on Neuroendocrinology—
  Dr. David C. Klein

Research activities involve environmental, pharmacologic, developmental, and biochemical factors critical to the metabolism and function of the pineal gland. Current studies on this model of neural and neuroendocrine regulation focus on the molecular mechanism involved in the transsynaptic adrenergic cAMP regulation of gene expression. In addition, control of reproductive physiology by the pineal gland is investigated.

Laboratory of Developmental Biology—
Dr. Igor Dawid

This laboratory consists of a group of scientists using the tools of molecular and cellular biology to answer questions about differentiation, development, and the control of genetic functions in simple and complex organisms. The range of model systems under investigation includes bacterial and animal viruses, tumor cells, differentiating immune cells, *Xenopus* embryos, and the fruit fly *Drosophila melanogaster.* Techniques employed range from bacterial, viral, and cell culture methods to gene isolation and recombinant DNA technology.

- Section on Developmental Biology—
  Dr. Igor Dawid
- Section on Molecular Regulation—
  Dr. Michael Cashel
- Section on Molecular Structure—
  Dr. Jacob V. Maizel, Jr.
- Section on Microbial Genetics—
  Dr. Robert Weisberg
- Section on Animal Viruses—
  Dr. Heiner Westphal

Developmental Pharmacology Branch—
Dr. Daniel W. Nebert

The molecular mechanisms underlying genetic differences and environmental factors affecting drug metabolism are investigated. Interests of the branch span from recombinant DNA technology and biophysical characterization of membrane-bound and cytosolic enzymes, to the use of mammalian model systems, especially the inbred mouse and rat, to projects in clinical pharmacology.

- Section on Pharmacogenetics and
  Molecular Teratology—
  Dr. Daniel W. Nebert

Studies are concerned with the development of methods *in vitro* and in cell culture for the assessment and prediction of the teratogenic, toxic, mutagenic, or carcinogenic effects of exogenous or endogenous compounds in animal model systems and in man. Developmental curves and the expression of genes controlling drug-metabolizing enzymes are studied, and the transplacental inducing effect of drugs, chemical carcinogens, mutagens, and other environmental pollutants are investigated as possibly important factors in the etiology of birth defects.

National Institute of Dental Research

John F. Goggins, D.D.S.,
Acting Director
Marie U. Nylen, D.D.S.,
Dr. odont., h.c.,
Director, Intramural Research
Bruce J. Baum, D.M.D., Ph.D.,
Clinical Director

The National Institute of Dental Research recruits about two or three dental and one or two medical staff fellows each year. Initial assignments are for 2 years and may be extended for a third year. Appointments usually begin on July 1. Selection of candidates is based on program needs and qualifications of candidate. The chiefs of branches and sections screen applications, carry out personal interviews of candidates, and make recommendations to the clinical director, who will make final selection. Selection of candidates for research positions will be made following personal interviews by chiefs of laboratories and branches who have vacancies occurring within their programs. After results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical and basic research program areas and the names of the program chiefs are listed below. A brief sketch of the clinical research areas is provided. Prospective applicants desiring more information should write to Dr. Marie U. Nylen, Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, MD 20205.

Dental Staff Fellows

Dental staff fellows spend much of their first year (about two-thirds) providing a wide range of care for patients at the Clinical Center. The remaining time is spent in clinical or laboratory research. The second (and third) year will be spent primarily (about 80 percent) engaged in supervised research with some clinical care responsibilities. Dental staff fellows must have a dental licensure in the United States, a minimum of 1 year hospital dental experience, and a desire for a career in academic dentistry.

Medical Staff Fellows

The medical staff fellow is assigned to one of the clinical research programs within which he or she carries out both clinical and laboratory studies. In addition, the medical staff fellow is responsible for performing medical evaluation and followup of patients accepted under one of the Institute's research protocols. Medical staff fellows may also be assigned to one of the basic research laboratories where they devote all their time to participating in laboratory research. One year of internship and at least 1 year of residency should be completed before the appointment begins.

Clinical Research Branches

Diagnostic Systems Branch—
Dr. Richard L. Webber

Investigations are directed toward research and development of diagnostic techniques. Specific emphasis is placed on radiologic and other noninvasive analysis techniques. Main focus is on interdisciplinary investigations linking clinical expertise with technical competence to facilitate a systems approach to diagnostic problems. Diagnostic systems are designed, modeled, and evaluated with the use of digital simulation techniques. Prototype systems are then developed and tested clinically. Bases for improvement include matching of system elements, image enhancement and new geometric bases for quantitative analysis of tissue morphology.

Neurobiology and Anesthesiology Branch—
Dr. Ronald Dubner

- Neural Mechanisms Section—
  Dr. Ronald Dubner

Research on peripheral and central nervous system mechanisms of oral-facial sensation is performed by this laboratory. In one major study, behavioral responses in monkeys trained in pain and temperature discrimination tasks are correlated with single-cell neuronal activity recorded at various levels of the trigeminal system. Other research involves combined neurophysiologic and anatomical studies of the organization of the spinal cord dorsal horn using the intracellular horseradish peroxidase method and light and electron microscope analysis of structural correlates of neural function.

- Neurocytology and Experimental Anatomy Section—
  Dr. Stephen Gobel

This section uses a variety of anatomical approaches to study how noxious inputs, which are transmitted by primary trigeminal neurons, are processed in the central nervous system. Major efforts are directed at the study of the morphology, synaptic connections, and development of second-order interneurons and projection neurons in the medullary (trigeminal nucleus caudalis) and spinal doral horns, as well as the identification of the major sources of brain stem descending inputs to these neurons. In addition, a series of experiments are being conducted in which the effects of peripheral nerve transection on synaptic connections are studied.

- Clinical Pain Section—
  Dr. Ronald Dubner

This group conducts research on the assessment of acute and chronic pain and the evaluation of new pain control methods. In psychophysical studies, verbal descriptor scales and metric analog scales are used to measure experimental and clinical pain responses in normal subjects and chronic pain patients. These scales also are employed to assess post-surgical pain and the effects of endogenous pain-suppressing mechanisms. Other studies include the development and application of sedative agents and techniques used in the control of anxiety and apprehension in patients. Research includes physiologic, pharmacologic, and psychologic studies of the efficacy and toxicity of combinations of intravenous sedative drugs used in extensive ambulatory surgical procedures.

National Caries Program: Caries Prevention and Research Branch—
Dr. William Bowen

- Biometry Section—Ms. Janet Brunelle
- Community Programs Section—
  Dr. Herschel Horowitz
- Etiology Section—Dr. Horace M. Stiles
- Preventive Methods Development Section—
  Dr. William H. Bowen, Acting

This branch investigates the etiology, pathogenesis and methods for the prevention of dental caries. Attention is paid to the factors that influence formation of dental plaque. The interaction of dietary constituents with the microbial flora of the mouth is studied. Emphasis is also placed on the natural defense mechanisms in the mouth by lactoferrin, lactoperoxidase, and antibodies as they relate to dental caries. Methods to enhance effectiveness of fluorides are explored. Epidemiologic studies of communities with unusual prevalence of caries are carried out. Clinical trials of caries preventive agents and research into improved methods of analyzing data are conducted.

Clinical Investigation and Patient Care Branch—
Dr. Bruce J. Baum

- Clinical Investigations Section—
  Dr. Bruce J. Baum
- Patient Care Section—
  Dr. Michael W. Roberts

This branch conducts laboratory and clinical studies on normal cellular regulatory mechanisms and alterations occurring in oral disease states. Particular emphasis is placed on exocrine secretion, bone formation and resorption, and white cell functions. Exocrine studies in salivary glands involve hormone/neurotransmitter-receptor interactions, signal transduction events (cyclic nucleotides, Ca^{++}, phospholipids), protein processing and translocation, and water and electrolyte secretion. Mineralization studies involve the isolation and characterization of factors that promote osteogenesis and the regulation, by various hormones, of osteoblasts. White cells are studied particularly as involved in periodontal diseases. Cell types studied include neutrophils, lymphocytes, and macrophages. Investigations focus on the regulation of one white cell type by another, the role of reactive oxygen species in immune responses, and probing the mechanism of activity of specific periodontopathic organisms utilizing monoclonal antibodies.

Basic Research Laboratories

Laboratory of Biochemistry—
Dr. Karl A. Piez

- Section on Protein Chemistry—
  Dr. Karl A. Piez

The emphasis of the program is on the chemistry and structure of collagen and its interactions with other connective tissue components. Biochemical and biophysical methods including high-resolution electron microscopy, nuclear magnetic resonance spectroscopy, and computer modeling are extensively used.

- Section on Enzyme Chemistry—
  Dr. John E. Folk

Enzymes called transglutaminases stabilize biological structures such as the fibrin clot and are involved in cellular processes by introducing covalent cross-links. Studies in this section are directed toward elucidating the mechanism of action and the biological significance of these enzymes.

- Section on Proteoglycan Chemistry—Dr. Vincent C. Hascall

Proteoglycans constitute a diverse group of connective tissue macromolecules consisting of both carbohydrate and protein. Their chemistry, structure, biosynthesis, and biological role are being investigated using organ and cell culture systems.

Laboratory of Biological Structure—
Dr. Arthur R. Hand

- Experimental Morphology Section—Dr. Arthur R. Hand
- Mineral Chemistry and Structure Section—Dr. Edward D. Eanes
- Skeletal Matrix Biochemistry Section—Dr. John D. Termine
- Bone Cell Biology Section—
  Dr. A. H. Reddi

The laboratory conducts basic research on the structural and chemical organization of the hard and soft tissues of the oral cavity. Major emphasis is directed toward elucidation of the chemical, physical, and biological mechanisms responsible for the differentiation, growth, and mineralization of bones and teeth. Other studies are concerned with the structure and function of exocrine secretory cells and the basic mechanisms of cellular secretion. Current investigations include: the structure, formation, and maturation of calcium phosphate salts; characterization of the extracellular matrix proteins of bones and teeth and their interactions with the mineral phase; factors regulating the differentiation and growth of endochondral bone and bone cell-matrix interactions; and glycoprotein transport, packaging, and secretion and membrane dynamics in secretory cells.

Laboratory of Developmental Biology and Anomalies—
Dr. George R. Martin

- Connective Tissue Section—
  Dr. George R. Martin

Research is directed toward the elucidation of teratogen-induced and inherited malformations. Projects include studying molecular mechanisms of cellular development, migration, and tissue formation and interaction. Drugs are used to probe these steps. Alterations in the production of such macromolecules as glycoproteins, collagen, and proteoglycans are also studied. Studies are under way on the regulation of gene activity using recombinant DNA technology. Our emphasis is on normal, mutant, fetal, and malignant cells from bone, cartilage, and other connective tissues. Medical staff fellows in this laboratory are encouraged to pioneer new research areas.

Laboratory of Microbiology and Immunology—
Dr. Stephen E. Mergenhagen

- Microbiology Section—
  Dr. Charles L. Wittenberger
- Cellular Immunology Section—
  Dr. Joost J. Oppenheim
- Humoral Immunity Section—
  Dr. Ann L. Sandberg
- Clinical Immunology Section—
  Dr. Reuben P. Siraganian

Research in microbiology focuses on bacterial ecology and pathogenesis, regulatory mechanisms in the metabolism of carbohydrates by oral bacteria, and on bacterial genetics, with emphasis on plasmid biology. The immunology programs consists of studies on the purification and properties of lymphokines and monokines which are involved in the induction of immunity and inflammation, the regulation of connective tissue metabolism by lymphocytes and macrophages, and the biochemistry of immediate hypersensitivity reactions. While a dental or medical staff fellow is assigned to one of the sections and will work under a senior investigator, considerable opportunity exists for collaboration with scientists in other components of the laboratory.

Laboratory of Oral Medicine—
Dr. Abner Louis Notkins

The laboratory conducts clinical research on diseases of the oral cavity. The interdisciplinary program emphasizes virology, oncology, and endocrinology. Present research projects focus on the molecular basis for recurrent and persistent viral infections (e.g., herpes simplex), with emphasis on recombinant DNA technology; the etiology and pathogenesis of leukoplakia and papillomas of the oral cavity; virus-induced immunopathology; the application of monoclonal antibody techniques to isolate viral variants; the influence of viral receptors in determining susceptibility to infection; the role of interferon in autoimmune diseases; the etiology of various dermatologic disorders including apthous ulcers; the role of viruses and immunologic factors in diseases of the exocrine glands (e.g., Sjögren's syndrome and salivary gland tumors) and endocrine glands (e.g., diabetes mellitus); and double-blind clinical trials to evaluate the effectiveness of various drugs in the treatment of oral lesions.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D.,
Director

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biologic factors in the environment that can adversely affect man; to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents; and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods, the interaction of multiple agents resulting in enhanced effects, and the modifying effects of variable physical and biologic states within man on the susceptibility to and course of disease induced by these agents.

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, North Carolina. NIEHS is the only one of the 11 Institutes comprising the National Institutes of Health located away from the campus in Bethesda, Maryland.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University of Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, seminars, and other scientific and professional activities associated with the universities.

Medical Staff Fellows

Medical staff fellows work at NIEHS under the direction of Dr. David Rall, Director, and a laboratory or branch chief in the Institute. Each fellow will work directly under a senior scientist in an area of research chosen by the fellow and the Institute. The initial appointment is for 2 years. These appointments are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. NIEHS does not have clinical facilities; however, medical staff fellows may work out informal arrangements with the clinical staff at the University of North Carolina and/or Duke University Medical School. Prospective applicants desiring more information should write to the Scientific Director, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709.

Intramural Research Laboratories

Laboratory of Pharmacology—

Dr. James R. Fouts

The toxic effects of low-level and/or chronic exposure to environmental constituents or contaminants on mammals and marine species are studied in this laboratory. Interactions (on or within the animal) of these environmental factors with each other and with drugs are also studied. Projects currently under way include: toxication-detoxication systems in the liver, lung, and skin and effects of pollutants on these systems and the balance between toxication and detoxication reactions; age-related changes in toxication-detoxication systems in various organs; uptake, storage, metabolism, and release of chemicals in the lung and liver; species differences in xenobiotic disposition and metabolism; and studies on the formation and metabolism of reactive metabolites of hydrocarbons in various marine species and purification and comparison of components of toxication-detoxication systems in various organs.

Laboratory of Reproductive and Developmental Toxicology—

Dr. Robert L. Dixon

Scientific efforts are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis with *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratology potential; study the molecular mechanisms underlying cellular differentiation; evaluate perinatal aspects of enzymology, endocrinology, and pharmacokinetics with regard to environmental toxicity; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects that do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of toxicity with the use of *in vitro* cells and tissues, lower animals, and biochemical test systems.

Laboratory of Behavioral and Neurological Toxicology—

Dr. Clifford L. Mitchell

Research is concerned with the study of changes in behavior and neurologic function produced by long-term exposure to low levels of many chemical and physical agents present in the environment. Special consideration is being given to the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurologic abnormalities, studies concerning the mechanisms whereby environmental factors produce behavioral and neurotoxic effects, and studies concerning the conditions that predispose individuals to the behavioral and neurotoxic effects of environmental factors.

Laboratory of Pulmonary Function and Toxicology—
Dr. Paul Nettesheim

The long-range objectives of this laboratory are to obtain through animal studies information needed to provide the scientific basis for the prevention of respiratory diseases which might have an environmental etiology. The intramural program is studying mechanisms of pulmonary biology and pathology in appropriate experimental models. Research is being pursued in pulmonary endocrinology, prostaglandins, biochemical pathology, environmental carcinogenesis, pulmonary cell biology, and pulmonary pathology.

Laboratory of Environmental Biophysics—
Dr. Colin F. Chignell

This laboratory is involved in several studies on the biologic effects of physical factors in man's environment. At present, the programs concentrate on biologic effects of microwave radiation and noise, singly and in combination with other factors. The effects of microwaves on reproduction and nerve functions (isolated nerves and activities of the central nervous system as reflected in behavior) are under study. Noise effects on various inner ear functions are being studied in combination with ototoxic drugs and heavy metals. New methods have been developed for quantifying microwave doses and for studying sound effects on inner ear physiology and biochemistry. Sophisticated spectroscopic techniques are used to study the molecular interaction of environmental agents with biologic systems.

Laboratory of Environmental Chemistry—
Dr. James D. McKinney

This branch supports research programs and collaborates with Institute laboratories on studies on the chemistry of suspect environmental agents. The branch utilizes, develops, and improves analytical methodology for specified agents which includes immunoassay and instrumental methods such as mass and magnetic resonance spectrometric techniques and high-pressure liquid chromatography. Suspect environmental agents and their conversion products are synthesized and characterized. Research studies on environmental agents, biological materials, and their metabolites emphasize biomechanism elucidation.

Laboratory of Animal Genetics—
Dr. Burke Judd

This laboratory concentrates on studies on the genetic structure of populations and on the structural and functional organization of higher eukaryotic genes, using model systems such as *Drosophila* and cultured mammalian cells. A group in genetic enzymology seeks to develop rapid and efficient methods for the purification of specific macromolecules, proteins, and nucleic acids. One project in chemical genetics focuses on the analysis of mutant mammalian proteins and DNA using primary sequence analysis.

Laboratory of Molecular Genetics—
Dr. John W. Drake

Research in this laboratory is concerned with the chemical nature of the mutation process, especially the nature of the initial damage to or spontaneous alteration of DNA and its subsequent enzymatic processing. Genetic and biochemical analyses are used with both prokaryotic systems and model eukaryotic systems such as yeasts and cultured mammalian cells. The laboratory also provides general services for other laboratories, such as prokaryotic chromosome mechanics, including recombinant DNA and strain synthesis. Studies aimed at developing or improving microbial screening systems for detection of chemical mutagens are also pursued.

Laboratory of Biochemical Genetics—
Dr. Heinrich V. Malling

This laboratory is concerned with studying mechanisms for induction of mutations in mammalian cells *in vivo* and *in vitro*; development and validation of test systems for detecting mutations in both mammalian somatic and germinal cells; correlating mutation induction with physiologic and biochemical endpoints; and, ultimately, facilitating evaluation of risks of exposure of human populations to environmental mutagens. Research is done on characterizing markers for mutation, such as monospecific fluorescent antibodies for mutant hemoglobin and mutant enzymes in sperm, and refining and validating automated systems, such as the cell sorter, for monitoring mutations in larger numbers of samples.

Biometry and Risk Assessment Program—
Dr. David G. Hoel

The Biometry and Risk Assessment Program conducts basic and applied environmental health oriented research in the areas of risk assessment, statistics, biomathematics, and epidemiology. In addition it assumes responsibility for data management and statistical analysis in the Toxicology Research and Testing Program, and provides statistical, mathematical, data processing, and computer engineering support to the other programs of the Institute. Organizationally, the program is divided into a Statistics and Biomathematics Branch, an Epidemiology Branch, and Computer Technology Branch.

Statistics and Biomathematics Branch—

The Statistics and Biomathematics Branch conducts a broad research effort ranging from statistical analysis to biomathematical modeling aimed at developing new or improved methods for quantitative risk estimation, particularly in the areas of carcinogenesis, mutagenesis, and reproduction. Branch scientists also maintain an active research program in statistical methodology relevant to design and analysis issues arising in laboratory experimentation with special emphasis on toxicological screening assays.

Epidemiology Branch—

The Epidemiology Branch initiates field studies of human disease, particularly chronic disease, due to environmental pollutants. The branch also investigates the effects of environmental toxins on fetal and child development and conducts basic and applied research in laboratory support methodology involved in the monitoring of human populations.

Computer Technology Branch—
Thomas A. Clemmer, M.S.

The Computer Technology Branch operates the Institute's computer systems and provides programming consultation services, including software systems development, to Institute personnel. It also maintains an active computer engineering group and furnishes systems analysis and project management support to various groups throughout the Institute.

Toxicology Research and Testing Program—
Dr. John A. Moore

The Toxicology Research and Testing Program—the NIH operating component of the National Toxicology Program—develops, validates, and evaluates methods for toxicity testing of chemicals and other environmental agents; is responsible for toxicity testing, using both short- and long-term bioassays, to determine or ascertain toxicity of chemicals and other environmental agents; coordinates and communicates test development and testing programs with other government agencies; and disseminates results of research, testing, methods development, and validation efforts to the scientific and public communities and to the regulatory agencies.

National Institute of General Medical Sciences

Ruth L. Kirschstein, M.D.,
Director
Sara A. Gardner, Ph.D.,
Director, Pharmacology
Research Associate Program

Pharmacology Research Fellowships

The National Institute of General Medical Sciences (NIGMS) has 11 positions (medical staff fellow and staff fellow) available each year for pharmacology research training. Those who are appointed begin on July 1 and are offered 2 years of postdoctoral training in a laboratory of a participating Institute of NIH under the Pharmacology Research Associate Program. The program seeks to develop scientists in pharmacologic research who will be leaders of the field in the future.

The program is directed to those persons who have already made a commitment in pharmacology by training or research in the field.

Fellows will engage in research relating principles of pharmacologic sciences to contemporary biomedical problems. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, physics, and instrumentation is also available. During their tenure, pharmacology research fellows devote the larger portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities.

Professional growth is achieved through the process of personal guidance by senior NIH scientists who are preceptors. A variety of laboratory problems and research approaches are designed to advance the work in progress and the competence of the prospective independent investigator. Preceptors and research fellows are matched by a mutual selection procedure after personal interviews. Candidates for pharmacology positions include those who will have received either the Ph.D., M.D., or equivalent degree and have research experience in areas relevant to pharmacology. They may also include those with research experience in a related area but who wish to further their development in pharmacology. Applicants with an M.D. degree may use this opportunity to further their training in basic pharmacologic research in preparation for a career in clinical pharmacology or a related discipline. Many NIH Institutes participate in this pharmacology research fellowship program.

Clinical Pharmacology

An opportunity is available for research training specifically in the area of clinical pharmacology. Applicants for research training in clinical pharmacology should have the M.D. degree, a minimum of 1 year, preferably 2, of graduate medical training (internship, residency), and a demonstrated interest in clinical pharmacology. The successful applicant will participate in a developing 2-year program under the guidance of several groups of investigators who are actively engaged in clinical pharmacological research in the Clinical Center, NIH. These preceptors will include but are not limited to:

Dr. Bruce Chabner, Chief,
  Clinical Pharmacology Branch,
  National Cancer Institute
Dr. Michael Ebert, Chief,
  Section on Experimental Therapeutics,
  National Institute of Mental Health
Dr. Stephen Epstein, Chief,
  Cardiology Branch, National Heart,
  Lung, and Blood Institute
Dr. James Gillette, Chief,
  Laboratory of Chemical Pharmacology,
  National Heart, Lung, and
  Blood Institute
Dr. Frederick Goodwin, Chief,
  Clinical Psychobiology Branch,

National Institute of Mental Health
Dr. Harry Keiser, Clinical Director,
National Heart, Lung, and
Blood Institute
Dr. Irwin Kopin, Chief,
Laboratory of Clinical Science,
National Institute of Mental Health
Dr. Charles Myers, Chief,
Biochemical Pharmacology Section,
Clinical Pharmacology Branch,
National Cancer Institute
Dr. Daniel Nebert, Chief,
Developmental Pharmacology Branch,
National Institute of Child Health
and Human Development
Dr. Snorri Thorgeirsson,
Laboratory of Carcinogen Metabolism
National Cancer Institute

Dr. William Z. Potter, intramural clinical pharmacologist, will serve as coordinator of the fellow's overall training in clinical pharmacology. The program emphasizes laboratory methods applicable to pharmacologic research in man but also includes training in general clinical pharmacologic principles (clinical pharmacokinetics and pharmacodynamics, biostatistics, drug evaluation, drug epidemiology, etc.).

The clinical pharmacology fellow's research experiences will be planned individually to meet the needs dictated by previous training, experience, and career goals. This research experience will involve both laboratory and human investigation.

A training plan, including formal course work, for each fellow will be developed by the Pharmacology Research Associate Program. A series of seminars will be organized with the participation of the clinical pharmacology fellows to ensure that their needs are met. Fellows may also help develop and instruct in the medical student elective program in clinical pharmacology.

In addition to a primary involvement in clinical pharmacologic research, the fellow will participate in clinical pharmacology rounds. These rounds will be directed on an alternating basis by preceptors from the different categorical areas to ensure a broad exposure to a wide range of problems in clinical pharmacology. Part of the clinical pharmacology experience will be collaborating with the coordinator in clinical pharmacology consultations for the Clinical Center.

An applicant may be considered for both the regular pharmacology research fellowship program and the clinical pharmacology option. Further information may be obtained from the Pharmacology Research Associate Program, NIGMS, NIH, Westwood Building, Room 919, Bethesda, MD 20205.

Program Areas

Choice of program area depends on the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request as a preceptor any senior scientist at the NIH, with the approval of the Pharmacology Research Associate Advisory Committee. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities.

National Cancer Institute

Laboratory of Chemical Pharmacology—

- Pharmacokinetics and Pharmacodynamics Section—
  Dr. Daniel S. Zaharko

This section is involved with pharmacologic investigations of cancer chemotherapeutic agents. Research efforts are currently directed toward altering the selectivity of known anticancer drugs by linking them to synthetic polymers and by using them in conjunction with normal intermediary metabolites such as nucleosides, amino acids, or vitamins. Most studies are carried out in rodent species and involve pharmacokinetics, radioactive tracers, *in vitro* enzyme inhibition, and tumor growth inhibition.

The research interests of this section are the relationship between pharmacokinetics and drug effects, the biochemical selectivity of anticancer agents in different organs and tissues, and the transport and role of nucleosides in the biochemical balance of the whole animal.

Laboratory of Carcinogen Metabolism—
Dr. Snorri S. Thorgeirsson

Investigations are conducted on: (1) the metabolic processing of various classes of chemical carcinogens, such as aromatic amines and amides; (2) the relationship between chemically induced mutations and carcinogenesis; (3) control of gene expression during chemically induced tumor formation; and (4) the role of modifiers of differentiation in the inhibition or promotion of tumor formation.

Clinical Pharmacology Branch—
Dr. Bruce A. Chabner

Our laboratory is concerned with the mechanism of action, pharmacokinetics, and mechanisms of resistance for the antimetabolite classes of antineoplastic drugs. Our primary interest at present is the process of metabolic conversion of antifolic compounds to polyglutamate metabolites. This conversion produces an intracellular metabolite which has different pharmacokinetic and biochemical properties from the parent compound and which appears to extend the duration of action of the drug. We have also been concerned with the clinical pharmacology of methotrexate, specifically with the use of test doses to predict drug clearance and to modify the doses in patients who receive high risk forms of methotrexate therapy. Other projects which our laboratory has recently completed include studies of mechanisms of antifolate resistance in cloned human tumor cells, determinations of cytotoxicity for the cytidine class of antimetabolites (cytosine arabinoside), and the mode of action of fluoropyrimidines. We are also collaborating in studies of the role of the pineal hormone, melatonin, in determining the risk of development of breast cancer in experimental models. These studies of melatonin physiology are conducted in conjunction with Dr. Marc Lippman's laboratory (Medicine Branch) and Dr. Larry Tamarkin of the NICHD.

Laboratory of Experimental Therapeutics and Metabolism—
Dr. Michael R. Boyd

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is in analytical and clinical pharmacology; qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents are studied in experimental systems, as well as in man in a clinical setting. Problems in this area are selected for their relevance to the development and/or evaluation of new chemotherapy protocols, and frequently are pursued collaboratively with other NCI laboratories. The other major research area of the section concerns the elucidation of fundamental chemicobiologic interactions underlying chemical-induced cytotoxicity and carcinogenicity to specific target organs and target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target tissue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic "activation" and "deactivation" systems are ongoing, as well as investigations of the biochemical, physiologic, and morphologic consequences of the *in situ* generation of alkylating metabolites both in normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemical-induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimal toxicity to normal tissues.

Laboratory of Medicinal Chemistry and Biology—
Dr. David G. Johns

This laboratory conducts an integrated program for the rational development of antitumor agents, carries out the synthesis of compounds with potential antitumor activity, and assesses the effects of such agents on experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites—nucleic acids, cell membranes, and microtubular protein and enzyme systems. Of special concern are agents that act as "stoichiometric" or "titrating" enzyme inhibitors, with current emphasis on the interaction of 2′-deoxycoformycin with adenosine deaminase and on the biochemical and pharmacologic effects of 2′-deoxycoformycin when used in combination with adenosine analogues. Another area of current interest is the maytansine group of mitotic inhibitors and the nature of their binding with microtubular protein.

Laboratory of Medicinal Chemistry and Biology—
Dr. Marco Rabinovitz

Attention is focused on the development of approaches for the potentiation of cancer chemotherapeutic activities. Nutritional and pharmacologic regimens are first explored in tissue culture and then extended to the tumor-bearing animal in attempts to direct cytotoxic agents toward the tumor cell and away from sensitive normal tissues. New cytotoxic and potentiating agents are also synthesized to achieve this goal. Biochemical studies include the analysis of inhibition kinetics of binding, transport, and detoxification of cytotoxic agents in sensitive and resistant tumor cells and in sensitive host tissues. An investigator is encouraged to use several of the above methodologies in pursuit of the solution to a particular problem.

- Applied Pharmacology Section—
  Dr. Robert I. Glazer

This section conducts studies of the mechanism of action of anticancer drugs in both mouse and human tumor cells in tissue culture. Areas receiving the greatest emphasis include the synthesis and processing of ribosomal, messenger, and transfer RNA; the methylation of RNA and DNA; the synthesis and repair of DNA; and the metabolism of anticancer drugs by the tumor cell. The classes of drugs under investigation are nucleoside analogs, intercalating agents, and human interferon. The primary purpose of these studies is to relate the cytotoxicity of anticancer drugs, as assessed by soft agar cloning, with their mechanism of action at the molecular level. A variety of the most up-to-date methods utilized in molecular biology and pharmacology are employed in successfully carrying out these avenues of investigation.

- Drug Interactions Section—
  Dr. Theodore Gram

Research interests include the chemical and biochemical mechanisms involved in interactions between xenobiotics and biologic materials that result in toxic responses; the morphologic reaction to toxic response to determine if the morphologic alterations precede, coincide with, or follow toxicity; studies to determine whether toxicity is spontaneously reversible and what factors, if any, augment or diminish the toxicity; and investigations on whether toxicity exhibits organ specificity and, if so, how it might be explained. The Section on Drug Interactions is particularly interested in the role of drug oxidation and conjugation in the detoxification and toxication of xenobiotics. Past work has been oriented toward microsomal and cytosol enzymes of the liver, lung, and kidney in these phenomena. Studies with lung have been conducted in intact animals, the isolated perfused lung, slices from normal lung and lung tumors, tissue homogenates, and subcellular fractions. This group is also interested in the functions that tissue uptake, binding, metabolism, and clearance have in drug-related specific end-organ toxicity. Investigations are currently in progress to evaluate these questions since they relate to the serious and dose-limiting problems of pulmonary fibrosis associated with a number of oncolytic agents such as bleomycin, renal necrosis resulting from platinum compounds, and myocardial fibrosis associated with adriamycin.

National Heart, Lung, and Blood Institute

Cardiology Branch—
Dr. Stephen E. Epstein

The branch's research objectives are oriented primarily toward an elucidation of the physiologic and biochemical mechanisms responsible for control of both the normal and failing heart, as well as the effects of various pharmacologic interventions on the normal and failing heart. Projects include pharmacologic, physiologic, and biochemical studies in man and animals. Major emphasis is on the study of the mechanisms responsible for myocardial cell death in acute myocardial infarction and in determining the causes of angina pectoris. Related studies are devoted to therapeutic interventions with particular emphasis on the effects of calcium channel blocking agents. Emphasis is also placed on study of the biochemical mechanisms involved in actin-myosin interaction and in muscle contraction.

Laboratory of Chemistry

- Section on Physiological Chemistry—
  Dr. John J. Pisano

Normal and pathologic states in man are studied at the molecular level. Under investigation are neuroactive (enkephalins) and vasoactive peptides (bradykinin and angiotensin), precursor proteins of the peptides (kininogens), and the enzymes (kallikreins) involved in their biosynthesis and degradation. Modern analytic techniques such as gas chromatography, high-performance liquid chromatography, affinity chromatography, mass spectrometry, and radioimmunoassay are commonly employed. Research is currently directed toward the discovery of naturally occurring biologically active peptides, the study of hypertension, new factors regulating coagulation and fibrinolysis, and micromethods for the detection and amino acid sequence analysis of polypeptides.

Laboratory of Chemical Pharmacology—
Dr. James R. Gillette

- Section on Drug-Enzyme Interaction—
  Dr. James R. Gillette

Various aspects of drug disposition are investigated, including the relationship between drug metabolism and drug toxicity. The main objective of this section has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. This section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal level.

Hypertension-Endocrine Branch—

- Section on Biochemical
  Pharmacology—Dr. Walter Lovenberg

Research is directed toward understanding the regulation of monoaminergic systems and the relationship of these systems to specific diseases. Both biochemical and pharmacologic approaches are used to investigate various neuronal systems and how information is transmitted between cells. This group is particularly interested in the role of cyclic nucleotides and calcium in these receptor-mediated responses. Some of the current research projects are: molecular characterization of the monoamine biosynthetic enzymes; regulation of catecholamine and serotonin synthesis by protein phosphorylation reactions; molecular events involved in the transduction of nerve impulses into changes in target cell proteins and enzyme levels in small blood vessels and the pineal gland; the distribution and physiologic role of the hydroxylase cofactor (tetrahydrobiopterin); the role of calmodulin in regulation of the activity of neuronal systems; the biochemical mechanism of antihypertensive and antipsychotic drugs; and the role of central and peripheral nervous systems in the regulation of blood pressure in experimental animals and man. The work encompasses several fields, including pharmacology, enzymology, protein chemistry, and molecular biology.

Laboratory of Biochemical Genetics—
Dr. Marshall W. Nirenberg

- Section on Molecular Biology—
  Dr. Marshall W. Nirenberg

Studies are conducted on clonal cells derived from the nervous system, including those of normal and neoplastic origin as well as somatic cell hybrids. The objective of this section are to identify molecules and reactions that enable cells to communicate with each other and to investigate the problem of how genes determine synaptic circuits when neurons are assembled into circuits during embryonic development. Work predominantly involves biochemistry and enzymology, mammalian cell culture, cyclic nucleotide enzymology, cell receptors, and enzymes of neurotransmitter metabolism.

Research is also directed toward the mechanism of action of opiate peptides, dependence and tolerance to these compounds, and the relationship of opiate receptors in the regulation of adenylate cyclase activity.

- Section on Macromolecules—
  Dr. Alan Peterkofsky

This section is concentrating on studies of cellular control mechanisms. One area of interest involves a study of the hypothalamic tripeptide, thyrotropin-releasing factor. The biochemical and pharmacologic properties of a newly discovered metabolite of thyrotropin-releasing factor are under investigation. These experiments may lead to a better definition of the metabolism and mechanism of action of this hormone. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells. Current information suggests that cyclic AMP concentrations in *Escherichia coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells.

Laboratory of Cellular Metabolism—
Dr. Martha Vaughan

The laboratory works on problems related to the control of cyclic nucleotide synthesis and degradation and the mechanisms of action of hormones and other agents that influence these processes in mammalian cells. Research in progress deals with cell-surface receptors, adenylate and guanylate cyclases, several cyclic nucleotide phosphodiesterases, cholera toxin, and ADP ribosyltransferases.

- Section on Cellular Pharmacology—
  Dr. Michael A. Beaven

This section has an interest in the study of drug action at the cellular level. Current work includes: studies on the mechanism of repression of lymphocyte blast transformation by anti-inflammatory drugs; the inhibition of white cell recruitment and chemotaxis in inflammatory reactions by anti-inflammatory drugs; release and metabolism of histamine and other active factors during inflammatory and allergic reactions; and studies with purified populations of cells from the gastric mucosa and capillary endothelial cells to determine distribution of histamine receptors and biochemical responses to histamine and other active hormones.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Laboratory of Bioorganic Chemistry—

- Section on Pharmacodynamics—
  Dr. John W. Daly

This section is engaged in research on the formation, degradation, and role of cyclic nucleotides in the nervous system—mechanisms that control adenylate cyclase and phosphodiesterases, receptors for catecholamines and other neurotransmitters, the relationship of membrane potential and generation of cyclic nucleotides, the interrelationship of adenosine and calcium in the regulation of cyclic nucleotide formation and action, morphologic entities associated with cyclic nucleotide formation and action, and the effect of drugs on neuronal function, in particular the transport and function of ions such as sodium, potassium, and calcium.

- Section on Pharmacodynamics—
  Dr. Phil Skolnick

The research program is concerned with understanding the relationship between receptors for psychoactive compounds and the endogenous substances which normally subserve these receptors. The techniques employed in studying these relationships range from biochemical investigations of the nature of endogenous ligands and their interaction with membrane receptors to the use of both primary and transformed cell culture models and classical "whole animal" pharmacology. Specific projects currently under investigation include: (1) differential regulation of CNS benzodiazepine receptors by pharmacologically defined "agonists" and "antagonists;" (2) study of the role of purines such as adenosine in modulation of central function through interaction with specific receptor sites; and (3) the physiologic and pharmacologic modulation of biogenic amine receptors and uptake systems in the CNS and the relationship to the functional role(s) of such receptors.

- Section on Oxidation Mechanisms—
  Dr. Donald M. Jerina

The primary interest of this section is the elucidation of the fundamental mechanisms by which drugs and environmental chemicals are transformed in the body. In many instances oxidative metabolism produces chemically reactive metabolites which are responsible for the cytotoxic, mutagenic, and carcinogenic activity of the drug substrate. Recent studies have been concerned with the roles of the cytochrome P-450 system and epoxide hydrase in the formation of mutagenic and carcinogenic metabolites from the polycyclic aromatic hydrocarbons. Emphasis is on modern instrumental techniques such as high-pressure liquid chromatography, high-resolution mass spectrometry-gas chromatography, and high-resolution magnetic resonance in the study of metabolism catalyzed by homogeneous enzymes.

Laboratory of Biochemical Pharmacology—
Dr. Herbert Tabor

Work in this laboratory is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biologic materials and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Current work is directed toward the mechanism and *in vivo* significance of these effects. The studies provide experience with a variety of techniques (enzyme characterization, bacteriophage, nucleic acid chemistry, and isotopic and nonisotopic synthesis). Special emphasis is placed in the use of plasmids and techniques involving DNA cloning, as well as on various genetic techniques in both *Escherichia coli* and in yeast.

Other work includes studies on control mechanisms for other enzymes in bacteria and in mammalian cell culture, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability. Studies are also carried out on developmental biology and organ regeneration in the rat and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

Laboratory of Biochemical Pharmacology—
Dr. Loretta Leive

This laboratory studies how structure is related to function in biological membranes. Phagocytosis in macrophages is being studied with two approaches: First, mutants of permanent macrophage cell lines unable to phagocytose have been selected and the biochemical changes responsible for these defects are being studied. Second, we have found that phagocytosis of bacteria by macrophages can be affected by slight changes in structure of bacterial surface polysaccharide; the effect of such changes on interaction with macrophages either directly or via complement activation is being studied. Bacterial membrane function is also being studied, specifically the outer membrane of gram-negative bacteria. This membrane admits small hydrophilic molecules but excludes larger hydrophobic ones, which is the opposite of most known biological membranes. Mutants altered in outer membrane components, or with increased permeability, are being used to analyze the mechanisms involved. Since exclusion of hydrophobic molecules causes resistance of gram-negative bacteria to antibiotics, the results may suggest ways to increase bacterial drug sensitivity.

Laboratory of Biochemistry and Metabolism—
Dr. William B. Jakoby

This group approaches the problems of detoxication at the level of purified enzymes. Proteins are brought to the stage of homogeneity and are studied with respect to catalytic, binding, and regulatory properties. Emphasis is on the mechanism of action. Current work is directed at those enzymes catalyzing reaction with glutathione, those effective in methylation, and those participating in sulfate conjugation.

Laboratory of Experimental Pathology

- Section on Cell Biology and Biochemistry—
  Dr. Harvey B. Pollard

The primary interest of this group is in mechanisms of secretion of proteins, hormones, peptides, and transmitters from neuroendocrine and other cells. The systems we are particularly interested in include islets of Langerhans, platelets, synaptosomes, and chromaffin cells. Critical problems now under investigation include how cytoskeletal proteins interact with subcellular organelles, how calcium acts to fuse secretory vesicles to plasma membranes, and how the release of vesicle contents during exocytosis subsequently occurs. The approach of this laboratory is to search for special proteins that could mediate such events; at present these include actin and synexin, a new protein that fuses secretory vesicle membranes exclusively in the presence of calcium. The interactions of these and related proteins with a wide variety of pharmacologic and environmental agents known to affect secretory processes are being analyzed.

Diabetes Branch—
Dr. Jesse Roth

The Diabetes Branch studies receptors for peptide hormones, especially insulin, insulin-like growth factors, and growth hormone. Current projects are focused on the role of receptors in disease states, receptor antibodies, and genetic disorders of glucose metabolism, isolation and characterization of receptor components, the role of receptors in hormone and drug action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects include insulin and insulin receptors in the central nervous system; the evolutionary origin of insulin, somatostatin, and other peptide messenger molecules; and their role in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

National Institute of Child Health and Human Development

Laboratory of Developmental Neurobiology—
Dr. Phillip G. Nelson

Research is conducted in neurobiology with the use of tissue cultures of normal and neoplastic nerve and muscle and various invertebrate preparations. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress. Biosynthesis and processing of a number of peptides of neurobiologic importance and the membrane mechanism of action of such peptides are under investigation. A primate vocal communication system in the squirrel monkey is being analyzed in behavioral and etiologic terms and with neurophysiologic techniques. Biochemical studies of inductive mechanisms in the nervous system are being done with the pineal gland and sympathetic ganglia.

- Section on Neuroendocrinology—
  Dr. David C. Klein

Investigations within the section focus on the molecular mechanisms through which hormones and biogenic amines regulate gene expression, with the primary experimental model being cultured pineal cells. Research is concerned with the relationship between biogenic amines and the production and release of hormones; emphasis is given to the study of β-adrenergic control of cyclic AMP and α-adrenergic control of cyclic GMP in pineal cells, and how these systems control metabolism. In addition, enzyme induction and activation is studied using drugs as biochemical and electrophysiologic tools to understand the intracellular reactions involved in large changes in enzyme activity. A second major area of interest is the factors regulating circadian rhythms; current investigations are concerned with the central neural mechanisms involved in generating daily rhythms in primates.

Developmental Pharmacology Branch—
Dr. Daniel W. Nebert

This branch investigates the interplay between genetic and environmental factors affecting drug-metabolizing enzymes. Molecular genetics and recombinant DNA technology are used to exploit the genetic regulation of drug-metabolizing enzymes among inbred mouse strains and cultured cells. The induction of these enzymes by drugs and other environmental agents, combined with underlying genetic predisposition of the individual animal, produce diverse responses seen in the research areas of pharmacology, toxicology, teratology, and chemical mutagenesis and carcinogenesis. The induction process involves drug receptors that are also under study. Data obtained from these experimental test systems are used to develop assays for predicting environmental diseases in human populations.

National Institute of Dental Research

Neurobiology and Anesthesiology Branch—

Dr. Ronald Dubner

This branch conducts studies on the neural basis of somatic sensation with an emphasis on pain mechanisms. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions. Electrophysiologic studies are concerned with the functional characteristics of single cells in the dorsal horn and their role in the coding of pain, temperature, and tactile information. In behavioral studies, monkeys are trained to discriminate noxious and innocuous thermal stimuli, and behavioral events are correlated with single-unit activity in the dorsal horn. The effects of various chemical mediators in brain on neural function and animal behavior are studied utilizing this behavioral model.

The clinical program of this branch conducts research on pain assessment and evaluates various pharmacologic agents utilized in the control of acute and chronic pain. Present studies include the development of new verbal descriptor methods for measuring experimental and clinical pain, the role of endogenous opiates in the control of postsurgical pain, the efficacy and toxicity of intravenous sedation methods used for ambulatory surgical procedures, and clinical trial studies on the analgesic potency of nonsteroidal anti-inflammatory drugs.

National Institute of Environmental Health Sciences

This Institute is the only one of the 11 Institutes that comprise the National Institutes of Health that is not situated on the campus in Bethesda, Maryland. It is located in Research Triangle Park, North Carolina.

Laboratory of Environmental Biophysics—
Dr. Colin F. Chignell

Research programs of the laboratory cover two main areas—the biological effects of some of the physical factors (nonionizing radiation, noise, and light) present in the environment and the use of physicochemical techniques to monitor the interaction of chemical and physical agents with various biological systems. The aim of the nonionizing radiation program is to develop new microwave exposure systems and to determine the effect of microwave exposure on human health. Current efforts include the effect of microwave radiation on the central nervous system and animal behavior, the cardiovascular system, the immunologic defense systems, and the fetus. The major effort of the noise program is directed towards elucidating basic mechanisms of noise-induced hearing loss, providing better methods for assessing such losses, and providing the means for accurately reproducing specific noise exposure environments. The remainder of the effort is focused on the reproductive, teratogenic, cardiovascular, and behavioral effects of noise. The light program is concerned with the mechanism of chemically induced photosensitivity and photoallergy. The effect of light of different wavelengths on the behavior and response of experimental animals to chemical agents is also being examined. The program in molecular biophysics mainly focuses on the use of sophisticated spectroscopic techniques (ESR, NMR, fluorescence and absorption spectroscopy, CD) to monitor the interaction of environmental agents with biologic systems. Current studies include the generation of free-radical intermediates during this metabolism of xenobiotics, the mechanism of mast cell degranulation, the binding of dyes to nucleic acids, and the interaction of metal ions with proteins and membranes.

Laboratory of Pharmacology—
Dr. James R. Fouts
Research Triangle Park, North Carolina

The research programs of this laboratory are concerned with relationships between the metabolism and translocation of chemicals and toxicity in various target organs (e.g., liver, lung, kidney, gut, and skin) or cells (e.g., Clara cells and alveolar type II cells of the lung). Pharmacologic, biochemical, physiologic, and pharmacokinetic concepts are used to elucidate the mechanisms by which environmental contaminants exert their toxic effects. Special areas of emphasis are: (1) those enzyme systems involved in the formation and detoxication of reactive metabolites, such as epoxides. An integrated approach is used in these studies and experiments are performed with purified enzymes (e.g., various cytochromes P-450), enriched cell populations isolated from several organs, isolated perfused organs, and intact animals, (2) the mechanisms whereby chemicals with hormonal activity alter the normal functions of liver, (3) the role of membrane structure and function in excretion and toxicity of environmental pollutants, and (4) the elucidation of reliable endpoints for the extrapolation of dose-dependent chemical effects across animal species and to humans.

The Comparative Pharmacology Section of this laboratory serves as a focal point within NIEHS for marine and freshwater biomedical research. This program is especially interested in the direct impact of pollutants present in the aquatic environment (including drinking water and aquatic animals) on human health. Mechanistic aspects of the accumulation, biotransformation, excretion, and toxicity of contaminant chemicals are studied in aquatic vertebrate and invertebrate species, frequently by comparison to similar processes in mammals.

Field laboratories are near St. Augustine, Florida, and in Salsbury Cove, Maine.

Laboratory of Reproductive and Developmental Toxicology—
Dr. Robert L. Dixon

Scientific efforts are directed toward the understanding of mechanisms of reproductive, endocrinologic, and developmental toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis using *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratogenic potential; determine the molecular mechanisms underlying cellular differentiation; study the molecular basis and determine the effects of environmental agents on endocrine function; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects which do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of reproductive, endocrinologic, and developmental toxicity using *in vitro* cells and tissues, lower animals, and biochemical test systems.

- Experimental Teratogenesis Section—
  Dr. Robert M. Pratt
  Research Triangle Park, North Carolina

Studies in this section deal primarily with embryonic and fetal development and the mechanism by which various environmental agents and drugs interfere with normal development. Emphasis is placed on the development of the craniofacial region and the biochemical and molecular basis for sensitivity to teratogens using cell, organ, and whole embryo culture in conjunction with biochemical, morphologic, pharmacologic, and toxicologic approaches. Of special interest is the manner in which various hormones and growth factors influence normal and abnormal development of embryonic and fetal tissues. Also of interest are the biochemical and molecular factors predisposing various strains of mice to the teratogenic and toxicologic effects of agents such as steroids and dioxins (TCDD).

Laboratory of Behavioral and Neurological Toxicology—
Dr. Clifford L. Mitchell

The research programs of the Laboratory of Behavioral and Neurological Toxicology cover three broad areas—the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurologic abnormalities, studies concerning the mechanism whereby environmental factors produce their behavioral and neurotoxic effects, and studies concerning the conditions that alter the responsiveness of individuals to the behavioral and neurologic effects of environmental factors. An interdisciplinary approach to these problems is taken utilizing behavioral, neurochemical, neurophysiologic, and neuropathologic techniques. Particular emphasis is placed on the behavioral and neurologic effects resulting from exposure to environmental agents during the development of the nervous system. Among the substances being studied are heavy metals, halogenated hydrocarbons, volatile solvents, microwaves, and their interactions with psychoactive drugs.

Laboratory of Pulmonary Function and Toxicology—
Dr. Paul Nettesheim

The research programs of the Laboratory of Pulmonary Function and Toxicology are concerned with the study of the cellular and biochemical basis of normal and abnormal lung functions. Special areas of emphasis are: (1) endocrinologic aspects of lung cell biology, the role of neuroendocrine cells in the lungs, their relationship to some hormonally active pulmonary neoplasms, and mast cell hormones; (2) metabolism of prostaglandins in the lungs and the effect of prostaglandins on some metabolic functions of the lung; (3) the composition, secretion, and function of the noncellular alveolar lining layer, particularly its protein components, and disturbances of the acellular alveolar lining layer in disease; (4) the biology, life cycle, and function of respiratory tract epithelial cells studied using *in vivo* and *in vitro* techniques; (5) the mechanisms of toxicity of airborne particles and fibers on lung tissues and the mechanisms of toxicity of asbestos studied *in vivo* and *in vitro*; and (6) mechanisms of respiratory tract carcinogenesis, the development of neoplastic disease, *in vitro* epithelial cell transformation and promotion studies, and mechanisms of cocarcinogenesis and promotion.

National Institute of Mental Health

Laboratory of Clinical Science—

- Section on Pharmacology—
  Dr. Julius Axelrod

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory also engages in examining control mechanisms of the biochemistry of the pineal gland, methylation reactions, and membrane structure and function.

- Section on Histopharmacology—
  Dr. David M. Jacobowitz

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic), cholinergic, gabaminergic, and peptidergic neurons in the brain, and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical, neurochemical, and physiological analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying basis for behavioral changes. Catecholamine histofluorescence, immunofluorescence, drugs, stress, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Neuronal amines, enzymes, and peptides are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence methods are also being used to study the localization of enzymes (DβH) and peptides (α-MSH, motilin, secretin, enkephalin, substance P pancreatic polypeptide) in the brain.

- Section on Medicine—
  Dr. Irwin J. Kopin

The research efforts of this section are centered around the study of biochemical and physiologic effects of drugs and toxins that alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes that control their synthesis in the central and peripheral nervous systems. The techniques used include radioisotopic methods (*in vivo* and *in vitro*), tissue slices, perfused organs, and organ and tissue cultures. Brain lesions and chronic indwelling catheters placed in arteries, veins, and cerebral ventricles are used in studies on animals. For application to clinical studies, procedures are developed to evaluate neurotransmitter and neuroendocrine function in human subjects with various neuropsychiatric disorders or during administration of psychoactive drugs. Plasma, urine, and cerebrospinal fluid are analyzed for various drugs, amines, and metabolites, and the rates of utilization or synthesis determined using radioimmunologic, enzymatic, or mass spectroscopic techniques.

- Section on Pharmacology—
  Dr. Martin Zatz

Current work is on problems in two areas: one concerns the mechanisms by which circadian rhythms are generated and regulated. The other concerns the identification, biosynthesis, and physiologic role of nonpolar methylated lipids in membranes. Biochemical and pharmacologic approaches to these problems are emphasized.

- Unit on Neuroendocrinology—
  Dr. Michael J. Brownstein

The members of this unit are trying to locate peptidergic neurons in the CNS and to characterize them anatomically. In addition, we want to learn how peptidergic neurons synthesize, transport, store, and release their biologically active products and hope to show how these processes are regulated by hormones and neurotransmitters.

Laboratory of Cerebral Metabolism—

- Section on Developmental
  Neurochemistry—Dr. Louis Sokoloff

Laboratory investigations are directed toward the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry to whole-animal physiology. Present emphasis is on the applications of a method recently developed in this laboratory that permits measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pathologic states.

Laboratory of Preclinical Pharmacology—
Dr. Erminio Costa

This laboratory conducts a program of research in neurochemical pharmacology directed to elucidate the molecular mechanisms that regulate production, metabolism and action of various putative neurotransmitters and the mode of action of various psychoactive drugs. Current research includes: the molecular regulation of postjunctional receptors for catecholamines, serotonin, GABA, acetylcholine, and polypeptides; the modification of the interactions between the neurotransmitters and endorphins and other neuropeptides elicited by long-term treatment with drugs; the use of stable isotopes to measure the turnover rate of acetylcholine, norepinephrine, dopamine, serotonin, and GABA by mass fragmentography in brain nuclei; the study of the mechanisms involved in the transsynaptic regulation of gene expression in neural cells; and the study of the heterogeneity of polypeptide neuromodulators in central and peripheral stores as an approach to understanding the regulation of their dynamic equilibrium.

- Section on Biochemical
  Pharmacology—Dr. Norton H. Neff

The concern of this section is with the effect of drugs on the biochemistry and physiology of the nervous system. Emphasis is placed on the biogenic amine-containing neuron. Current studies are directed toward the characterization of enzymes involved in amine metabolism, the biochemical evaluation of receptor responses, the evaluation of the mechanism of action of drugs that alter neuronal function, and the possible role of the biogenic amines in various disease states.

Laboratory of Neurochemistry—
Dr. Seymour Kaufman

The main effort of this laboratory is devoted to the metabolic interaction between the brain and its peripheral environment. Current research involves: 1) molecular characterization of phenylalanine, tyrosine, and tryptophan hydroxylases, enzymes that are rate limiting in the catabolism of phenylalanine and the biosynthesis of catecholamines and serotonin, respectively, 2) investigation of the regulation of these enzymes by cyclic nucleotide and calcium-dependent protein phosphorylation, 3) studies on the regulation of tetrahydrobiopterin biosynthesis, and the elucidation of physiologic roles for this compound other than as the essential cofactor for the aromatic amino acid hydroxylases mentioned above, 4) evaluation of the efficacy of pterin administration as therapy for human subjects with disorders of tetrahydrobiopterin metabolism and 5) determination of the biochemical basis for hypertrophy of muscle, a tissue that shares many cellular characteristics with brain. This work encompasses numerous fields including pharmacology, enzymology, protein chemistry, pterin chemistry, and physiology. In use are techniques as diverse as affinity chromatography, HPLC, brain lesions, and indwelling catheterization of veins and arteries. Experimental preparations include tissue slices, synaptosomes, organ and tissue cultures, and hepatocytes as well as purified enzymes.

Laboratory of General and Comparative Biochemistry—
Dr. Werner A. Klee

The major emphasis of the current program is directed toward the elucidation of the mechanism of action of opiates and the peptides that normally interact with opiate receptors. Included are studies on the isolation and characterization of opiate receptors and the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in culture, are aimed at understanding opiate tolerance and dependence in biochemical terms. In addition, the interrelationships among the several components of inhibitory-receptor adenylate cyclase couples, including especially GTP binding and hydrolysing proteins, are being explored. The relevance of this work to the action of other CNS-active drugs and to normal brain function is also being explored.

Biological Psychiatry Branch—
Dr. Agu Pert

This laboratory is concerned with analyzing the mechanisms of action of psychoactive drugs and neuropeptides in the brain and defining the neurochemical coding of brain circuits that control specific behaviors. Methods used include extracellular single-cell recording as well as iontophoretic techniques with drugs in specific brain regions. Lesion and microinjection procedures are then utilized to relate these effects to behavior. Our current emphasis is on two projects: the actions of endorphins and enkephalins on brain function, especially the processing of pain information, and the effects of lithium (a therapeutic agent in manic-depressive illness) on neurotransmitter receptor sensitivity.

- Section on Molecular Pharmacology—
  Dr. John F. Tallman, Jr.

Current investigations are directed toward an understanding of the regulation and actions of receptors at the cellular level. Two examples of current work are: interactions between GABA receptors and benzodiazepine receptors; the synergistic actions of these receptors on neuronal firing and biochemical parameters of cellular activity and benzodiazepine receptor purification; and mechanisms that control the number and functioning of β-adrenergic receptors in cultured cell lines and alterations in β-adrenergic receptors that occur following exposure of cells to β-adrenergic agonists (desensitization).

- Section on Neuronal Pharmacology—
  Dr. Candace B. Pert

The recent structural identifications of substance P and enkephalin have spurred our investigations of other neuropeptides (bombesin and vasointestinal peptide). Our primary interest is the characterization of receptors for neuropeptides and other psychoactive substances whose mechanism of action is currently unknown. Mapping the distribution of brain receptors (by *in vitro* autoradiography) currently with their endogenous ligands (by immunohistofluorescence) provides clues for elucidating interneuronal connections. Physiologic and/or pathologic states that greatly elevate plasma and/or cerebrospinal fluid levels of neuropeptides are sought to provide clues about normal function. Direct receptor binding techniques provide an approach for sorting out receptor heterogeneity on the basis of assocation with GTP-sensitive regulatory units, specific ionic effects related to receptor-coupled ionophores, and relative agonist or antagonist affinity.

Clinical Psychobiology Branch—

- Section on Clinical Pharmacology—
  Dr. William Potter

Clinical pharmacology, investigation into the neurotransmitter- and neuroendocrine-related mechanisms involved in primary affective disorders (bipolar and unipolar depression) and basic research on brain proteins, peptides, and receptors are major parts of an integrated effort in the psychobiology branch. In this section, double-blind drug trials are used to compare clinical response, neuroendocrine changes, drug pharmacokinetics, and measures of amine turnover and metabolism. Methodologies include rating of clinical change, determinations of hormone concentrations by radioimmunoassay, measurements of drugs and monoamine metabolites with gas chromatography or gas chromatography-mass spectroscopy, and use of tracer doses of radiolabeled drugs and amine precursors in man.

A metabolic inpatient unit and an outpatient drug treatment clinic provide the opportunity for longitudinal studies of clinical and biochemical changes. In addition, research is directed toward answering practical questions in therapeutics such as the use of loading doses to predict the ultimate steady-state therapeutic concentration of tricyclic antidepressants, and the use of biological and clinical measures as predictors of therapeutic response to specific drugs.

Neuroscience Branch

- Section on Preclinical Studies—
  Dr. Steven M. Paul

The major research interests of the section concern the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with neuronal membranes, including membrane receptors and ion channels. Wherever possible basic laboratory studies are applied to clinical problems. Several receptor systems are currently under investigation, including receptors for benzodiazepines, tricyclic antidepressants, serotonin, adenosine, and the neuropeptide cholecystokinin. The role and regulation of these systems are investigated by: (1) biochemical and pharmacological characterization of the recognition sites; (2) isolation and characterization of the endogenous modulators of these sites; (3) development of appropriate *in vitro* models for studying these receptors (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharamcologic experiments in animals; (6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor changes in correlation to the behavioral manifestations of these genetic mutations; and (7) postreceptor events, including calcium transport and cyclic nucleotide changes.

National Institute on Alcohol Abuse and Alcoholism

Laboratory of Preclinical Studies—
Dr. Forrest F. Weight

Research investigations in this laboratory center around the pharmacology of neurons and synapses in the central and peripheral nervous system. The general areas studied include: cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin, and GABA; membrane mechanisms of neurotransmitters and drug actions; cellular actions of peptides such as enkephalins, endorphins, and LH-RF; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbiturates, opiates, and other neuroactive substances. The research techniques available to a medical staff fellow include: extracellular unit recording and iontophoresis of drugs and putative transmitters to single neurons in the CNS; intracellular recording and intracellular injection techniques; use of *in vitro* preparations, such as CNS slices, sympathetic ganglia, and tissue culture for studying the pharmacology of drug-receptor interactions; voltage and patch clamp techniques for studying the ionic basis of membrane permeability changes involved in drug and transmitter actions.

National Institute of Neurological and Communicative Disorders and Stroke

Developmental and Metabolic Neurology Branch—

- Membrane Biochemistry Section—Dr. Peter H. Fishman

Our research involves the biosynthesis, organization, and function of cell surface membrane components. Of major interest are the mechanisms by which cells receive, process, and attenuate external signals. We are using the hormone-stimulated adenylate cyclase system as a model for transmembrane signaling. Hormones are recognized by specific receptors on the external side of the plasma membrane; following hormone binding, there is a transduction process which leads to stimulation of adenylate cyclase on the cytoplasmic side of the membrane. Prolonged stimulation results in both desensitization whereby the transduction process becomes attenuated and in down-regulation whereby the receptors become internalized and degraded. We are also exploring the biosynthesis of two classes of receptors, glycoproteins and glycolipids; how these receptors become integrated into the plasma membrane; how the receptors are turned over; and how the cell regulates these processes.

Experimental Therapeutics Branch—

- Biochemical Neuropharmacology Unit—Dr. John W. Kebabian

The Biochemical Neuropharmacology Unit studies the biochemical mechanisms underlying the activity of receptors for neurotransmitters. There is a special interest for dopamine receptors found in brain and simpler peripheral endocrine tissues. The knowledge obtained from simple endocrine tissues about the biochemical mechanisms underlying receptor function is applied to the brain.

- Physiological Neuropharmacology Unit—Dr. Judith R. Walters

Studies in the Physiological Neuropharmacology Unit are focused on investigation of neuronal interrelationships and drug interactions with neurotransmitter function in the CNS, especially in areas of the basal ganglia, including the substantia nigra, striatum, and globus pallidus. Extracellular single recording procedures and iontophoretic techniques are chiefly employed. Currently, the role of dopamine, GABA, and peptide-containing neurons in these brain regions are being investigated through neurophysiologic determinations combined with drug treatment, administration of selective lesions, and determination of biochemical parameters of transmitter function.

Laboratory of Neurophysiology—
Drs. Jeffery L. Barker and
Thomas G. Smith, Jr.

The principal aims of this laboratory are to understand how nerve cells communicate and how CNS-active drugs alter neuronal communications. The preparations used include the mammalian CNS grown in tissue culture and amphibian and molluscan nervous systems studied *in vitro*. The methods used are primarily electrophysiologic, including intracellular recording, voltage-clamp and patch-clamp techniques, and extracellular microiontophoresis. Specific projects include the comparison of neurotransmitter and peptide neurohormone functions at the single-cell and defined-circuit level; the cellular pharmacology of general anesthetics, convulsants, and anticonvulsants; and optical techniques applied to the analysis of neuronal function.

National Institute of Mental Health

Herbert Pardes, M.D.,
Director
Frederick K. Goodwin, M.D.,
Director, Intramural Research
Edward V. Evarts, M.D.,
Associate Director for Basic Research
Irwin J. Kopin, M.D.,
Associate Director for Clinical Research
Michael H. Ebert, M.D.,
Clinical Director

The National Institute of Mental Health (NIMH) offers an opportunity for postdoctoral research training in psychiatry and in the biologic and behavioral sciences. The NIMH intramural program is located on the NIH campus in Bethesda, Maryland, and in the William A. White Building, St. Elizabeths Hospital, Washington, D.C. Some medical staff fellows conduct clinical and/or basic research, and are responsible for the clinical care of patients admitted for research and therapeutic purposes. Other fellows engage primarily in laboratory research in the biologic or behavioral science laboratories under the preceptorship of the senior staff. All medical fellows participate in tutorial seminars and other teaching programs as their needs and desires indicate. Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all medical staff fellows to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Appointments in Clinical Research

The NIMH recruits about 12 new medical staff fellows each year who are primarily involved in laboratory research. Appointments normally begin July 1 and are usually for 2- or 3-year periods, although in some instances they may be extended.

Fellows usually begin their appointments after the PGY-4 level of residency training. Exceptionally well-qualified individuals, however, may be appointed after 1 or 2 years of training in psychiatry, neurology, or other clinical specialties. The Clinical Center is approved for 1 year of psychiatric residency training at the PGY-4 level.

Applications for the Medical Staff Fellowship Program are now being accepted only for July 1983 appointments. Since selections for these positions will be made in the spring of 1982, PGY-2 or PGY-3 psychiatric residents may now apply.

Medical staff fellows usually work in close association with senior clinician-scientists on one of the clinical research wards or in a clinical research laboratory. The first year is usually predominantly clinical with intense experience in the diagnosis and inpatient management of research patients, special clinical and administrative issues in a research setting, psychopharmacology, clinical research methodologies and design (by the initiation of at least one clinical research project under the direction of the senior clinician-scientist), and the psychotherapy and psychodynamics of research patients and their families. The following years focus primarily on research that may be clinical, clinical-biochemical, or laboratory, depending on the interests of the fellow and the status of the clinical research program. Intensive clinical supervision on the inpatient psychiatric unit is available from senior psychiatrists and consulting psychoanalysts. Candidates desiring more information about clinical fellow positions should write to Dr. Michael H. Ebert, NIMH, Building 10, Room 3N234, NIH, Bethesda, MD 20205.

Appointments in Laboratory Research

Some fellows work primarily in the laboratory under the preceptorship of a senior staff scientist. They are usually assigned to a basic science laboratory for intense training and experience in specific neurobiologic or psychosocial concepts and methodologies. For further information about these positions in the neurobiologic area, contact Dr. Irwin Kopin, NIMH, Building 10, Room 2D46, NIH, Bethesda, Maryland 20205. For information in the psychosocial area, contact Dr. Marian Yarrow, NIMH, Building 15K, NIH, Bethesda, MD 20205.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIMH programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in preclinical or clinical pharmacology. For more information about the PRAT program, see pages 70 through 85.

Biological Psychiatry Branch—
Dr. Robert Post, Acting

This branch conducts a broad program of research, training, and treatment of clinical psychiatric problems including schizophrenia, manic-depressive illness, drug abuse, and childhood mental illness. The focus of the branch is psychobiologic and brings together information from four disciplines—psychiatry, genetics, pharmacology, and biochemistry. Some specific research interests are psychogenetics, the biochemistry of neurotransmission, twins and siblings, investigations of perception and cognition, average evoked response, and studies of the physiology of sleep and sleep changes in psychiatric illness. A general goal of this branch is to develop programs to investigate biologic contributions to schizophrenia, manic-depressive illness, and childhood mental illness.

Fellows will be trained in clinical research methodology, data analysis, and clinical management of research patients.

- Section on Psychogenetics—
  Dr. Elliot S. Gershon

A research goal of this section is to identify familially transmitted biologic and behavioral characteristics associated with the affective and other major psychiatric disorders, including pharmacogenetic and genetic marker investigation. The section has a followup outpatient clinic for these studies. Other research goals are to identify the mode of genetic transmission, to separate out familial and nonfamilial factors in the liability to the disorders, to develop mathematical models of inheritance appropriate to psychiatric disorders, and to study neurobiologic characteristics in cell culture and DNA studies.

- Section on Psychobiology—
  Dr. Robert M. Post

This 12-bed psychiatric research unit focuses on the clinical and biologic assessment and treatment of patients with manic-depressive and schizoaffective illness and rapidly cycling phenomena. Medical staff fellows are research collaborators in a variety of studies of the interactions of psychological and biologic parameters in the psychoses and usually take responsibility for the design, conduction, and publication of several research projects. Mood, cognitive, and behavioral variables are viewed in relation to such biologic correlates as sleep, motor activity, evoked potentials, and endocrine function. Particular attention is given to the study in psychiatric patients of central amine metabolism with the use of CSF strategies, such as the measurement of amine metabolites, electrolytes, cyclic nucleotides, regulatory enzymes, and peptides in CSF. Work is closely coordinated with several biochemical laboratories. The mechanisms and time course of the biologic effects of psychotropic drugs are studied in relation to clinical response.

New pharmacologic agents are being tested, including dopamine receptor agonists, the anticonvulsant carbamazepine, and several endogenous polypeptides. The mechanisms underlying the paradoxic antidepressant effect of one night's sleep deprivation are being studied. Clinical and laboratory studies of psychomotor stimulants are ongoing. An active behavioral pharmacology laboratory is maintained for the study of the long-term effects of psychomotor stimulant administration and electrical kindling in rodents and primates as models for the development of psychosis.

- Section on Sleep Studies—
  Drs. J. C. Gillin and W. B. Mendelson

This unit is studying the sleep patterns of the patients on the clinical research units and in the sleep laboratory. In addition to phenomena associated with various disorders, emphasis is placed on the biochemical substrates of sleep processes, the response of patients to various pharmacologic alterations, neuroendocrine relationships, and memory.

- Section on Childhood Mental Illness—
  Dr. J. L. Rapoport

This unit operates on a four-bed day and/or overnight hospitalization inpatient program in collaboration with the Section on Experimental Therapeutics, Laboratory of Clinical Science, and independently on a pediatric ward maintained by NICHD. Current focus is on diagnostic assessment and drug treatment of hyperactive children. Drug studies include pharmacokinetic studies of drugs given to children and studies of kinetics and metabolism of neurotransmitter systems via body fluids.

Also under way are outpatient studies of obsessive-compulsive children, and the evaluation of children whose parents have been hospitalized here in the past for affective illness and offspring of alcoholics.

Clinical Neuropharmacology Branch—
Dr. Dennis L. Murphy

This branch conducts clinical and laboratory studies designed to contribute to the understanding of the mechanisms of therapeutic drug effects in individuals with affective disorders, obsessive-compulsive symptoms, and other behavioral disorders. The studies are primarily based on a 10-bed psychiatric research ward. The inpatient investigations are complemented by an outpatient program with an emphasis on psychobiologic studies of possible high-risk segments of a community population, directed by Dr. Larry Siever.

Support for the clinical studies includes a behavioral assessment and data processing program, as well as a biochemistry/neuroendocrinology laboratory under the direction of Dr. Robert M. Cohen. Other neurochemical laboratory studies are oriented toward cellular pharmacology using electron microscope approaches (Dr. Jonathan Costa) and toward neurotransmitter-related enzymes (Dr. Dennis L. Murphy). Facilities for small animal and nonhuman primate studies are also available in the Branch.

The ward research investigations, which are balanced between biologic-pharmacologic and psychological-phenomenologic approaches, take place in the setting of an active milieu treatment program. The incoming medical staff fellow, depending on his or her prior research and clinical experience, will usually participate at first in ongoing research projects and the clinical program. With increased experience, the fellow will work with a senior staff member in the planning, design, and implementation of one or more research projects to be initiated in the first year and completed in the second or possibly third year.

Emphasis is on the strategies and methods used in clinical research and laboratory approaches to clinical problems. Specific research projects range from psychological studies of the characteristics of individuals who do or do not respond to specific drugs and to laboratory or animal studies of the effects of drugs on cellular processes, including enzyme activity, membrane transport, and neurotransmitter receptor functions. Studies of psychoactive drug effects on neurotransmitter metabolism and neuroendocrine function are a particular focus in both the clinical and nonhuman primate areas.

Drugs currently under study include selective monoamine oxidase inhibitors, some natural precursors of brain neurotransmitters, and lithium carbonate, as well as other antidepressants and some new investigational compounds. Special areas of study at present include investigations of adaptational responses to longer-term drug administration in neurotransmitter receptors and secondary effector systems; animal models of affective disorders; neuroendocrine responses, and other characteristics differentiating subgroups of psychiatric patients; studies of monoamine oxidase; the development of new electron microscope-based techniques (e.g., energy loss spectroscopy) for the study of the storage and metabolism of neurotransmitter amines and other substances in cells; and methods for the assessment of behavioral and psychological states.

Clinical Psychobiology Branch—
Dr. William Potter, Acting

Clinical research is conducted in areas related primarily to affective illness (depression and mania) and its treatment. Laboratory research involves studies on the neurobiology of brain receptors, proteins, peptides, neurotransmitter amines, melatonin, and other neuroendocrine substances. Structurally the branch is divided into the Clinical Research Unit, the Unit on Neurochemistry and Preclinical Pharmacology, and the Outpatient and Follow-up Unit. Throughout the 2- to 3-year assignment, the fellow's time is divided among clinical care-ward management, clinical research, and laboratory research, depending on interest. Direct responsibility for research projects is assumed in the beginning. The branch is also responsible for research training in clinical and preclinical pharmacology through the Pharmacology Research Associate Program of the National Institute of General Medical Sciences.

- Clinical Research Unit—
  Dr. Thomas Wehr

This unit represents the major research resource of the branch and is located in a 15-bed psychiatric research ward. Ongoing clinical projects include the following: under the direction of Dr. Philip Gold, neuroendocrine strategies for the evaluation of hypothalamic-pituitary function are developed, and these measures are integrated with the study of amine metabolites from spinal fluid and urine. Clinical studies of vasopressin function are a major current focus. A wide range of consultation and collaboration with endocrine groups in other Institutes is afforded by Dr. Gold's full participation in the Interinstitute Endocrine Program. Studies of biological rhythms, under the direction of Dr. Wehr, involve clinical investigations of abnormalities in timing or phase of circadian rhythms in depression, mania, and certain sleep disorders. Using new techniques and instruments, circadian rhythms in motor activity, body temperature, REM sleep, plasma cortisol, melatonin, and other hormones are measured around the clock in patients and normal volunteers. Patients' responses to stimuli, such as light, that function as time cues which synchronize circadian rhythms with the day-night cycle are studied. Effects of antidepressants on the timing of circadian rhythm pacemakers in human and experimental animals are being studied. Clinical and biological effects of experimental manipulations of circadian rhythms with light and with sleep schedule alterations (including sleep deprivation) are investigated in patients and normal subjects. The clinical pharmacology of antidepressants, under Dr. Potter, is a special interest, including the development of pharmacokinetic models for predicting dose.

- Outpatients and Follow-up Unit—
  Dr. Rex Cowdry and
  Mrs. Yolande Davenport

A short-term evaluation and treatment program for acute depression constitutes the major focus of the clinic, which is closely integrated with the inpatient unit. The clinic is also involved with the maintenance treatment and long-term evaluation of recurrent affective disorders. Studies of "well state" are integrated into prophylactic drug trials; the interaction between psychotherapy and drug therapy is a special interest. A study of the borderline syndrome, exploiting biological abnormalities, is under way.

A complete list of the branch's current research projects is available on request.

Neuroscience Branch—

The branch conducts a multidisciplinary program in basic and clinical neuroscience and attempts to integrate data on the biochemistry and pharmacology of the central nervous system with an understanding of the pathogenesis and treatment of major psychiatric diseases. Structurally the Neuroscience Branch consists of four sections: Clinical Neuroscience, Molecular Pharmacology, Neuronal Biochemistry and Preclinical Studies. Medical staff fellows are assigned to the clinical research unit, usually for a period of two to three years. During this time their activities are divided between direct patient care, clinical research, and laboratory research, depending on the interests and talents of the individual. Medical staff fellows will be encouraged to become actively involved in ongoing research projects, as well as to develop their own research protocols as early as possible. Collaborations between individual medical staff fellows and the three basic science sections, on both laboratory and clinical research projects, will also be encouraged. The overall goal of the branch is to create a climate in which sound scientific findings can be applied to an understanding of both normal and abnormal behavior.

- Section on Clinical Neuroscience—
  Dr. Steven M. Paul, Acting

The Clinical Neuroscience Section consists of a 12-bed clinical research unit which is primarily involved in clinical and laboratory research on acute and chronic schizophrenia. A major emphasis is on the psychobiology of this illness, including pharmacologic, biochemical, and genetic aspects. Attempts at delineating patient subgroups and correlating biological phenomenon with these subgroups is a major focus of many of the current research protocols. Outpatient studies will focus on the psychopharmacologic and behavioral management of schizophrenic patients, including attempts at understanding the factors responsible for relapse.

- Unit on Neuropsychopharmacology—
  Dr. Daniel P. van Kammen

Current areas of interest involve the study of the role of dopamine and norepinephrine in schizophrenia and the use of drugs with specific actions on dopamine and norepinephrine metabolism. Metabolites of neurotransmitters and enzymes are being assessed in the urine, plasma, and cerebrospinal fluid (CSF). Other areas of interest involve attempts to delineate vulnerability markers (state-independent and state-related variables); the prediction of antipsychotic drug response and prognosis; exploration of GABA, neuropeptides (such as endorphins and vasopressin), and other neurotransmitter systems for their potential involvement in psychosis; evaluation of new antipsychotic drugs; assessment of pharmacologic and endocrinologic aspects of schizophrenia and schizoaffective illness; immunologic aspects of schizophrenia; study of CAT scan abnormalities; cognitive and psychophysiologic evaluations, and PET scan studies.

- Unit on Clinical Studies—
  Dr. David Pickar

This unit encompasses the entire inpatient evaluation and treatment of patients on the clinical research unit. Current research problems include investigations of the clinical phenomenology of schizophrenia and the similarities and differences between schizophrenia and schizoaffective disorders. Studies on the role of central and peripheral opioid systems (i.e., enkephalin, β-endorphin) in stress, schizophrenia, and patients with acute and chronic pain are also ongoing. Laboratory investigations on possible peripheral biological markers in schizophrenia, as well as various affective disorders (i.e., platelet [^{3}H] imipramine binding, serotonin transport, RBC membrane fluidity), are being carried out in hopes of unraveling vulnerability factors in these disorders.

Laboratory of Clinical Science—
Dr. Irwin J. Kopin

This laboratory conducts research on the biochemistry, physiology, and pharmacology of the nervous system and relates these findings to clinical areas in medicine, neurology, psychiatry, and anesthesiology. Applicants for the medical staff fellow program in laboratory research should have at least 1 year of clinical training, whereas those interested in clinical research are required to have at least 2 years of postdoctoral training in neurology or psychiatry before arrival for duty.

The research program objectives are attained through the cooperative efforts as well as the independent research of investigators in the various sections and units of the laboratory.

- Section on Pharmacology—
  Dr. Julius Axelrod

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory examines control mechanisms of the biochemistry of the pineal gland and membranes.

- Section on Histopharmacology—
  Dr. David M. Jacobowitz

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic) and cholinergic and gabaminergic neurons in the brain and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical and neurochemical analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying bases for behavioral changes. Using the catecholamines histofluorescence method, the study of drugs, stress, and surgical stereotaxic lesions is used to correlate changes in neuronal function with various parameters of behavior. Behavioral studies being pursued involve the genetic fat rat, spontaneous hypertensive rat, sexual and reproductive function, and various stress manipulations. Neuronal amines, enzymes, and peptides are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence and radioimmunoassay are also being used to study the localization of enzymes (DβH) and peptides (α-MSH, bombesin, enkephalin, vasopressin, substance P, and pancreatic polypeptide) in the brain. Studies of peptides in human and animal brain and cerebrospinal fluid are currently under way. These are designed to examine the dynamics of release of peptides within the brain.

- Section on Medicine—
  Dr. Irwin J. Kopin

The research efforts of this group center around the study of biochemical and physiologic effects of drugs and toxins that alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes that control their synthesis in both the central and peripheral sympathetic nervous systems. The techniques used include radioisotopic methods *in vivo* and *in vitro,* tissue slices, perfused organs, and organ and tissue cultures. Brain lesions, direct stimulation of specific areas in the brain, chronic indwelling catheters placed in arteries, veins, or cerebral ventricles, are used in studies in animals. Procedures are developed for application to clinical studies for evaluation of neurotransmitter and neuroendocrine function in human subjects. These studies are carried out in cooperation with other clinical units and include various disorders of the autonomic nervous system (orthostatic hypotension, hypertension, familial dysautonomia), neuropsychiatric disorders (Korsakoff's syndrome, Huntington's disease), as well as the major psychoses. Plasma, urine, and CSF are analyzed for various drugs, amines, and metabolites and the rates of utilization or synthesis determined using radioimmunologic, enzymatic, or mass spectroscopic techniques.

- Section on Experimental Therapeutics—
  Dr. Michael H. Ebert

The section conducts studies of the clinical pharmacology of a variety of neuropharmacologic agents, including amphetamine and phencyclidine. Neurochemical, neuroendocrine, and pharmacokinetic experiments and drug trials are in progress in a variety of neuropsychiatric and psychosomatic syndromes. The section operates a clinical research unit to pursue these studies. In collaboration with other investigators in the Laboratory of Clinical Science, experiments are in progress in primates and man to measure turnover rates of brain monoamines by stable isotope labeling techniques and changes in synthesis rates produced by disease states and/or pharmacologic treatment. Diseases of interest at the present time include orthostatic hypotension, anorexia nervosa, several presenile dementias, and hyperactivity in children.

- Unit on Pharmacological Applications of Mass Spectrometry—
  Dr. Sanford P. Markey

The unit develops techniques for clinical studies of neurotransmitters, neurohormones, peptides and their metabolites, and drugs that influence their formation or disposition. Projects include the synthesis of stable isotope-labeled analogs of amines and metabolites for human kinetic studies, the isolation and quantitative assay of compounds of interest, and the design and construction of alterate ion sources for mass spectrometry. Current projects include the synthesis of ^{18}O-dopamine as a probe of peripheral norepinephrine metabolism in humans; the negative ion mass spectral quantitation of levels of melatonin in plasma and its alteration by disease and pharmacologic intervention; and the assay of the major urinary melatonin metabolite for developmental studies in neonates, infants, children, and in patients with disorders of the sympathetic nervous system or who receive drugs influencing the sympathetic nervous system.

- Unit on Neuroendocrinology—
  Dr. Michael J. Brownstein

The members of the unit are trying to locate peptidergic neurons in the central nervous system and to characterize them anatomically. In addition, investigations on how peptidergic neurons synthesize, transport, store, and release their biologically active products are in progress. The focus of these studies is to show how these processes are regulated by hormones and neurotransmitters.

Laboratory of Developmental Psychology—
Dr. Marian Radke-Yarrow

This program conducts research on the behavioral development of children, primarily affective and social development, and on interrelations between stressful conditions—biomedical or psychosocial—and the functioning of children. There is an emphasis on research strategies and methods in the investigation of child behavior. Variables such as mood, aggression, altruism, and social cognition are of special interest. Laboratory studies, as well as field studies, are conducted on children, infants through adolescents. Much of the research is collaborative, involving investigators in other laboratories of NIMH and other Institutes. Specific projects include studies of early problem aggression, developmental continuity and discontinuity in affective and social characteristics of children, effectiveness of various therapies for different types of problem behavior in children, and child rearing environments and their consequences for children. Among the risk groups being studied are children reared by parents with affective disorders. Biomedical conditions studied in relation to behavior include juvenile diabetes, chronic malnutrition, cancer, and hormonal abnormalities.

Laboratory of Psychology and Psychopathology—
Dr. Allan F. Mirsky

This laboratory conducts a broad program of basic and clinical research on attention, learning, and memory in both humans and monkeys and on the neurophysiologic and psychophysiologic mechanisms involved in these processes.

Studies on the neurophysiology of attention in monkeys with single unit recording from various parts of the brain and with stimulation and ablation techniques are focused on the investigation of animal models of cognitive processes that may be impaired in many human psychiatric and neurologic disorders. Parallel studies of cognitive processes in psychiatric and neurologic patients and in normal controls using similar behavioral techniques are designed to permit direct comparison with the animal work.

Studies of memory functioning in a wide variety of patients and of pharmacologic influences on memory in humans are being conducted by Dr. Herbert Weingartner. Studies of attention and autonomic nervous system functioning in schizophrenics and in other patients and drug effects on these processes are being done by Dr. Theodore P. Zahn. Investigations of attention and cortical and brainstem averaged evoked potentials in psychiatric and neurologic patients are under way.

Division of Biological and Biochemical Research—
Dr. John C. Eberhart

Laboratory of Neurobiology—
Dr. Ichiji Tasaki

Current research projects include electrophysiologic, bio-mechanical, and biochemical studies of the mechanism of nerve excitation. By using extremely sensitive mechanical devices constructed in the Laboratory of Neurobiology, mechanical changes associated with action potentials in nerves are being analyzed. These changes are interpreted in terms of structural changes in the axolemma-ectoplasm complex of nerve.

Another major project in this laboratory involves a developmental study of the appearance of excitability in nerve and muscle cells grown in culture. This project involves studies of excitability at three levels of cellular organization: binding studies using a variety of toxins known to affect excitability, studies involving the uptake of sodium by the cells in response to a variety of drugs and toxins, and electrophysiologic responses of the cells to various drugs and toxins. The goal of this work is to understand how these cells become excitable and, thus, the biochemical mechanism of excitability.

Laboratory of General and Comparative Biochemistry—
Dr. Giulio L. Cantoni

Investigations are concerned with the mechanisms and pathways of biological methylation, alkaloid biosynthesis, opioid peptides, cellular differentiation, and gene expression in eukaryotes. The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, mechanism of drug addiction, muscle differentiation in cell culture, and genetic engineering.

- Section of Alkaloid Biosynthesis—
  Dr. S. Harvey Mudd

This section studies the enzymes involved in biosynthesis in methylation in plants and their control. The section also studies enzymatic mechanisms of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

Laboratory of Cerebral Metabolism—
Dr. Louis Sokoloff

- Section on Developmental
  Neurochemistry—Dr. Louis Sokoloff

A broad program of investigation is conducted on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds such as hormones that play important physiologic roles in CNS function. A method recently developed in this laboratory permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic, pharmacologic, and pathologic states.

Laboratory of Neurochemistry—
Dr. Seymour Kaufman

The following areas are studied: the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine-hydroxylating system. In addition to studies with the pure enzymes, emphasis is placed on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia. This laboratory investigates the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin, the relationship between the properties of the enzymes, and physiologic regulation of rates of synthesis of these neurotransmitters; the biochemical basis for skeletal muscle hypertrophy, including the effects of exercise and neural factors in the process; cell-surface membrane proteins and receptors in their role in cellular differentiation; and the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

Laboratory of Neurophysiology—
Dr. Edward V. Evarts

This laboratory conducts research on neural control of movements, plasticity of stimulus-response relations, and anatomic and histochemical correlates of brain activity.

The studies on neural control of movement are designed to elucidate the functional interrelations between motor subsystems (spinal cord, brain stem, cerebellum, basal ganglia, thalamus, and cerebral cortex). This work involves behavioral, electrophysiologic, and neuroanatomic techniques. Projects are aimed at understanding reflex and voluntary motor function. Studies on the control of eye movements focus on the vestibulo-ocular reflex and on saccadic movements. Discharges of single nerve cells are recorded with microelectrodes in monkeys trained to carry out movements, and the results are interpreted in relation to the anatomic input-output properties of the loci from which recordings are obtained.

Work in the area of plasticity of stimulus-response relations involves the role of segmental and suprasegmental neural factors in determining the modifications of muscular activity associated with motor learning in man and subhuman primates. Studies also focus on mechanisms underlying adaptive changes in the vestibulo-ocular reflex in the monkey.

Changes of neuronal activity are associated with anatomic and histochemical alterations. Studies are currently focused on the nature of these alterations in relation to circadian rhythms and motor activity.

Laboratory of Brain Evolution and Behavior—
Dr. Paul D. MacLean

Opportunities are offered for research on evolutionary, developmental, ethologic, and ecologic factors relating to brain function and behavior. Large outdoor and indoor habitats are available for comparative studies on reptiles, birds, and mammals living under seminatural conditions. The laboratories are equipped for neuroanatomic research, microelectrode recording, brain stimulation, and psychological testing and have a computer system with high-speed graphics capability for the recording and processing of electrophysiologic and behavior data. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted, species-typical behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior.

Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, ethology, psychology, ecology, paleobiology, and systematics. The laboratory is located at the NIH Animal Center near Poolesville, MD.

Division of Special Mental Health Research—

Dr. Richard J. Wyatt

This division, located at Saint Elizabeths Hospital, conducts a program of intramural research on special mental health problems, such as psychopharmacology, neuropharmacology, neuroanatomy, sleep, memory, normal and abnormal human behavior, and geriatric psychiatry. Clinical evaluations, treatment and followup are an integral part of all research protocols.

- Adult Psychiatry Branch—
  Dr. Richard J. Wyatt

This clinical research laboratory capitalizes on many disciplines in its effort to understand and treat schizophrenia, the psychiatric problems of the elderly, central nervous system regeneration, memory, sleep, and its disorders. The laboratory is set up so that small groups of young scientists may employ biochemical, structural, anatomic, pharmacologic, physiologic, and psychologic techniques in their work with these basic science and clinical problems.

- Clinical Director—
  Dr. Llewellyn B. Bigelow

The major focus of the branch's research takes place on three inpatient research wards. There is substantial opportunity to examine drugfree patients and to use pharmacologic probes to discern different patient groups. Three 12-bed research wards housed in the William A. White Building are devoted to schizophrenia research. There is also an outpatient department for studying geriatric psychiatry and schizophrenia and a day hospital. In addition, many of the 1,800 inpatients at Saint Elizabeths Hospital participate in research programs.

- Group on Animal Behavior—
  Dr. David Stoff

Using a wide range of paradigms in a diverse group of animals, behaviors are monitored to understand basic processes and pharmacologic issues, such as tolerance to drugs, experimental diets, and interactions of drugs with one another and with hormones.

- Group on Mass Spectrometry—
  Dr. Farouk Karoum

The laboratory operates two quadruple mass spectrometers which are primarily used in clinical studies to measure neurotransmitters and their metabolites. A major current interest is measuring phenylethylamine (PEA), an endogenous amphetamine-like compound which has been suggested to be elevated in the urines of some paranoid schizophrenic patients.

- Group on Receptors—
  Dr. Jack Rosenblatt

This group has been instrumental in developing and using radioreceptor techniques for clinical studies. The group actively uses radio-ligand, neuroleptic, and benzodiazepine assays, as well as measuring a diverse group of receptors in human brain and peripheral tissues.

- Group on Cell Culture
  Dr. Steven Zalcman

This group uses cell culture techniques to enhance our knowledge about potential abnormalities on human peripheral tissues. The group interacts closely with the groups studying receptors and enzymology.

- Enzymology and Cell Sorting Group—
  Drs. Bruce Phelps and Lynn DeLisi

This group is principally interested in evaluating the significance of decreased activities of the enzymes monoamine oxidase and dopamine-beta-hydroxylase, both of which have been reported to be altered in some schizophrenic patients. Clnical data and biological samples from patients and their relatives are routinely analyzed with the aim of understanding the significance of deficits in these enzymes. In addition, the group has a fluorescence-activated cell sorter (FACS III) being used to examine structural differences in various cellular samples (particularly lymphocytes) from schizophrenic patients. Subtle differences in immune systems of these patients are being systematically studied using the FACS. Other cell types are being sorted on the basis of differential binding of fluorescent compounds for further use in tissue culture and animal experiments.

- Group on Geriatric Psychiatry
  Drs. Peter Bridge, David Shore, and Dilip Jeste

This group is actively carrying out clinical studies in geriatric patients with psychiatric illnesses. These include depression, alcoholism, Alzheimer's disease, and tardive dyskinesia. Current studies in depression are attempting to look at pharmacokinetics and to evaluate psychotherapy versus tricyclic antidepressants in a geriatric population. Alcohol studies are being carried out in conjunction with scientists in the Alcohol Institute, in an attempt to understand psychologic and physiologic changes that occur with chronic drug abuse in older individuals. A principal hypothesis about the etiology of Alzheimer's disease is that aluminum deposits accumulate on the DNA of the brains of patients with Alzheimer's disease. This group is currently carrying out a project to determine whether or not decreasing aluminum in the body of patients with Alzheimer's disease has any effect on the course of this illness. Tardive dyskinesia is a principal and serious side effect of the clinical use of neuroleptic drugs. It is far more common in older patients than younger ones. This group is currently trying to determine both the etiology and how we can best prevent tardive dyskinesia in patients who must be on these drugs for long periods of time.

- Brain Grafting and Nerve Regeneration Group—
  Drs. William J. Freed and Luis de Medinaceli

This group emphasizes the exploitation of brain grafting techniques to correct lesion-induced behavioral deficits. Currently under study are the characteristics of the brain as a site of transplantation and the potential of brain grafts to effect functional reconstitution. A major success has been in grafting adrenal medulla or substantia nigra to the caudate nucleus, thereby correcting the rotational behavior that develops following unilateral substantia nigra lesions. Destruction of the substantia nigra has been considered by many to be an animal model of Parkinson's disease, and this group is applying these techniques to rats and monkeys in order to develop brain grafting within this model. Other related interests involve the transplantation of endocrine and retinae to the rat brain.

Although fiber sprouting is always observed following peripheral nerve injury, the functional consequences of such injury are variable, and, in mammals, functional recovery is frequently slow and incomplete. This group is interested in developing new approaches to peripheral nerve repair, in order to improve the rate and degree of functional recuperation, and to better understand the mechanisms involved in promotion and obstruction of peripheral nerve regeneration in mammals.

- Brain Neuroanatomy and Neurochemistry Group—
  Drs. Janice R. Stevens, Daniel R. Weinberger, and Joel E. Kleinman

This group is investigating the relationship of behavior and psychopathology to neuroanatomic and neurochemical alterations in the brains of patients with neuropsychiatric disorders, principally schizophrenia. In living subjects, the emphasis is on linking brain structure, metabolism, and function to develop more meaningful dimensions of psychiatric syndromes. Powerful new techniques that are currently utilized include computed tomography (CT), xenon-133 regional cerebral blood flow, and positron emission tomography (PET).

A large human brain bank is the focus of postmortem studies that are evaluating neurochemical, immunologic, and virologic hypotheses of neuropsychiatric illness. Current projects include qualitative and quantitative neuroanatomy, immunocytochemistry, and studies of biogenic amine, peptide, and receptor neurochemistry.

- Unit on Sleep Studies—
  Drs. J.C. Gillin and W.B. Mendelson

This unit is studying the sleep patterns of the patients on the clinical research units and in the sleep laboratory. In addition to phenomena associated with various disorders of sleep, such as insomnia, narcolepsy, sleep apnea, and phase lag syndrome, studies of traditional psychiatric illnesses such as depression and schizophrenia are performed. Emphasis is placed on the biochemical substrates of sleep processes, circadian rhythms, the response of patients to various pharmacologic alterations, neuroendrocine relationships, and memory.

Laboratory of Preclinical Pharmacology—
Dr. Erminio Costa

Scientific efforts of this laboratory are directed toward the elucidation of neuronal control mechanisms that mediate responses of drugs affecting neuronal function. The laboratory is organized into one group and four sections.

- Group on High-Pressure Liquid Chromatography—Dr. James Meek

New methods are developed to investigate drug effects on renovation rates of brain stores of monoamines and neuropeptides.

- Section on Molecular Pharmacodynamics— Dr. Darwin Cheney

Pharmacologic studies are conducted on the dynamics of acetylcholine in discrete brain nuclei using pulses of deuterated precursors and mass fragmentography, the dynamics of GABA in discrete brain nuclei using pulse labeling with ^{13}C glucose and mass fragmentography, and the regulation of the dynamics of acetylcholine and GABA by various endogenous neuropeptides.

- Section on Biochemical Pharmacology—Dr. Norton Neff

This section conducts investigations directed at the identification of control mechanisms for enzymes that regulate the dynamics of putative brain neurotransmitters and the determination of drug actions on the regulation of turnover rate of brain monoamines using mass fragmentography.

- Section on Neuroendocrinology— Dr. Alessandro Guidotti

Studies concern the molecular mechanisms involved in the transsynaptic induction of tyrosine hydroxylase and the activation of cAMP-dependent protein kinases in relation to the neuroendocrine control of pituitary and pineal glands.

- Section on Molecular Neurobiology— Dr. Erminio Costa

Investigations are conducted on the regulation of nerve growth factor production by glial cells; the role of chromatin phosphorylation in the regulation of gene expression; the pharmacology of binding of putative neurotransmitters to postsynaptic receptors; the regulation of storage, release, and synthesis of peptides that function as putative neurotransmitters (enkephalins, substance P, angiotensin, and neurotensin); and the identity and kinetic properties of enzymes that regulate the synthesis and metabolism of neuropeptides.

National Institute of Neurological and Communicative Disorders and Stroke

Murray Goldstein, D.O., M.P.H.,
Acting Director
Thomas N. Chase, M.D.,
Director, Intramural Program
Richard L. Irwin, Ph.D.,
Laboratory Director

Appointments in Clinical Research

Medical staff fellow positions for the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) are available in medical and surgical neurology, experimental therapeutics, infectious diseases, neuroimmunology, and developmental and metabolic neurology. Fellows are appointed for 2 years, with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on NINCDS wards, involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NINCDS research emphases.

Candidates requiring further information about NINCDS clinical positions for medical staff fellows should write to Dr. Thomas N. Chase, Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 36, Room 5A05, NIH, Bethesda, MD 20205.

Appointments in Laboratory Research

NINCDS medical staff fellow positions are available in molecular biology, neurochemistry, neurophysiology, neuropathology, and other areas of fundamental neuroscience investigation. Appointments are for 2 years, with the possibility of extended affiliation.

Areas of study are developed by each fellow in conjunction with a preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned. Independence and originality of approach are encouraged.

Medical staff fellows have the opportunity to work closely with a large and diverse group of senior investigators, to participate in on-site courses and conferences, and to employ advanced neuroscience technology in the conduct of their research.

For further information on the NINCDS Medical Staff Fellowship Program, write to Dr. Thomas N. Chase, Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 36, Room 5A05, NIH, Bethesda, MD 20205.

Medical Staff Fellows in Epidemiology

Intramural Research Program—
Dr. Thomas N. Chase
- Section on Neuroepidemiology—
  Drs. Bruce S. Schoenberg and
  Roswell Eldridge

The section conducts national and international studies concerning the patterns of neurologic disorders in human populations. Both environmental and genetic factors in disease etiology are considered. The medical staff fellow receives training in the utilization of neuroepidemiologic and neurogenetic techniques to the solution of practical problems in clinical neurology and neurosurgery. Although the section's program involves the application of epidemiologic methods to the study of any disorder of the nervous system, current research concentrates on cerebrovascular disease, brain tumors (including neurofibromatosis), dementia, cerebral palsy, torsion dystonias, multiple sclerosis, parkinsonism, and racial differentials in the occurrence of neurologic disease.

Clinical Branches

Clinical Neurosciences Branch—
Dr. Susumu Sato

Various clinical and electroencephalographic (EEG) aspects of seizure disorders are investigated, with emphasis on localization. Cerebral evoked response techniques are also applied for clinical seizure research. EEG and cerebral evoked response examination are provided for patients referred from the entire Clinical Center. The appointment of medical staff fellows (with preference for persons with experience in clinical neurology) is for 2 years. Basic investigation is focused on pathophysiologic aspects and pharmacologic aspects utilizing a kindling model of epilepsy. Medical staff fellows are appointed for 2 years. Preference is given to persons with some experience in the fields of electrophysiology and/or electronics or neuroanatomy.

Developmental and Metabolic Neurology Branch—
Dr. Roscoe O. Brady

- Section on Enzymology and Genetics—
  Dr. Roscoe O. Brady

Principal research efforts concern the pathologic biochemistry, diagnosis, carrier identification, and genetic counseling related to inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, Krabbe's disease, and Tay-Sachs disease, along with the development of enzyme purification procedures for replacement therapy trials. Other studies include alterations of complex lipid metabolism in neoplastic cells and the role of trophic hormones with cell membrane receptors.

- Section on Neurochemical Methodology—Dr. Andrew E. Gal

This section is involved in the preparation of widely useful substrates for the facile diagnosis of metabolic disorders, the development of ultramicroanalytic procedures for monitoring the effects of enzyme replacement therapy, and the synthesis of novel lipids and lipid analogs for metabolic studies in normal and pathologic tissues.

- Section on Myelin and Brain Development—Dr. Richard H. Quarles

Research is primarily concerned with the composition and metabolism of myelin components in the developing nervous system and an examination of abnormalities of their structure and function in demyelinating conditions such as multiple sclerosis.

- Section on Physiology and Metabolism—Dr. Eberhard G. Trams

Principal research involves the delineation of the molecular basis of nerve excitation as related to structural and functional sidedness of natural and artificial membranes.

- Section on Membrane Biochemistry—
  Dr. Peter H. Fishman

Research is directed towards the biosynthesis, organization, and function of cell membranes including transmembrane signaling of receptor-mediated information, regulation of membrane enzymes, biogenesis of membrane components, and topologic organization of cell-surface receptors.

- Section on Clinical Investigations and Therapeutics—
  Dr. John A. Barranger

Investigations are concerned with heritable and acquired disorders of metabolism, with emphasis on the elucidation of pathogenetic mechanisms and the development of measures for the treatment of these conditions including replacement of enzymes in deficiency disorders.

Experimental Therapeutics Branch—
Dr. Thomas Chase, Acting

- Section on Therapeutics—
  Dr. Donald B. Calne

The major effort of this section is directed at the development of drugs to improve the treatment of parkinsonism; in particular, agents that modify dopaminergic transmission are under investigation.

- Section on Pharmacology—
  Dr. Thomas N. Chase

This section is primarily concerned with the generation of new strategies for the pharmacotherapy of choreatic and dyskinetic disorders by the manipulation of neurotransmitter activity.

- Section on Clinical Epilepsy—
  Dr. Roger J. Porter

  The major effort of this section is the intensive monitoring of patients with uncontrolled seizures by videotape recordings and telemetered electroencephalography, the study of the metabolism and efficacy of various antiepileptic agents, and studies on the usefulness of new scanning procedures, such as positron emission tomography.

- Unit of Biochemical Neuropharmacology—Dr. John Kebabian

  Research is conducted on the biochemical properties of synaptic receptor mechanisms in the central nervous system (CNS) and drug-induced modification of receptor activity.

- Unit of Physiological Neuropharmacology—Dr. Judith Walters

  Measurements are undertaken to evaluate the effects of drugs on the electrical discharges of single nerve cells in various regions of the CNS.

Infectious Diseases Branch—
Dr. John Sever

- Section on Immunochemistry and Clinical Investigations—
  Dr. Sidney Houff

  The pathogenesis of multiple sclerosis, Epstein-Barr virus infections, amyotrophic lateral sclerosis, and progressive multifocal leukoencephalopathy is under study. Persistent perinatal infections are also being investigated. The role of viruses and cellular immune responses in patients and experimental animals is being tested. Clinical work is done on abnormal antibody and cellular immune reactions in these patients.

- Section on Neurovirology—
  Dr. Maneth Gravell

  This section is involved in research on viruses as causes of tumors of the brain, Reye's syndrome, and cerebellar disease with infectious mononucleosis (Epstein-Barr virus), as well as experimental models of persistent virus infections. Methods include tissue culture, cocultivation, new tests for cellular immunity, and antibody determinations.

- Section on Experimental Pathology—
  Dr. W. T. London

  Studies of perinatal infections that cause birth defects and persistent central nervous system infections are conducted in monkeys and small laboratory animals. Papovaviruses, cytomegaloviruses, toxoplasmosis, and herpes viruses are being used. Methods for direction, treatment, and prevention are being developed. Practical applications include vaccine development, rapid diagnostic tests, and assessment of new antimicrobial agents.

- Section on Electron Microscopy—
  Dr. Monique Dubois-Dalque

  This section uses high-resolution scanning electron microscopy and immunoperoxidase labeling to study mechanisms of acute and chronic infection of disassociated infected nerve cells; interactions between antibodies, lymphocytes, and the surface of virus-infected cells; and the brains of animals and patients with acute and chronic viral infections and/or demyelinating diseases.

One medical staff fellow is appointed annually for 2 years. This individual participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as fellows for a 2-or 3-year period. These individuals perform basic research relevant to neurologic disease.

Surgical Neurology Branch—
Dr. Paul L. Kornblith

This branch investigates and treats clinical problems of disordered neuronal and glial proliferation and differentiation. A major part of the program is devoted to the study of intracranial tumors including pituitary tumors. Problems of both central and peripheral neuronal and glial regeneration are also under study. Clinical research in these areas is combined with basic techniques of cell biology, tissue culture, biochemistry, immunology, pharmacology, and light and electron-microscopic histology to provide for an in-depth exploration and, ultimately, new approaches to these problems.

The mechanism of pain sensation is currently investigated in the neurophysiology laboratory. The responses of the nerve cells at different levels in the CNS are recorded in animals with extracellular or intracellular microelectrodes and pharmacologic agents are applied through micropipettes.

Experimental neuropathology and neuroimmunology is emphasized in a program which includes clinical diagnostic neuropathology. Biochemistry, morphology, and immunochemistry of neoplasms are studied as means of improving detection and treatment and as clonal models of their nonneoplastic counterparts in nervous and lymphoid tissues.

Studies are being carried out on cell-mediated immune mechanisms in human brain tumor patients, including delineation of the effectiveness of various forms of cell-mediated immunity to contribute to the destruction of brain tumors, examination of the ability of brain tumors to elicit cellular immune responses both *in vivo* and in model systems *in vitro,* and exploration of possible modes of altering brain tumor cells so as to increase their immunogenicity. This work is complemented by studies in animal models on basic mechanisms of cell-mediated immune lysis of tumor cells.

The medical staff fellow participates in the care of patients on the various protocols of the Surgical Neurology Branch as well as consultative care of patients with neurosurgical problems in all the NIH Institutes. The fellow receives training in the diagnostic and operative techniques of surgical neurology with special emphasis on microneurosurgery both in the animal laboratory and in the operating room. In addition, there will be opportunity for work in the laboratory with training in a wide range of cell biology techniques, with special emphasis on tissue culture, immunoneurology, and electron microscopy. Experimental surgery and other therapy in animal models as it relates to the clinical problems under study will also be performed. The fellow also works in collaboration with senior scientists or independently in specific laboratory areas as his or her experience and interest dictates.

- Section on Neuroradiology and Computed Tomography—
  Dr. Giovanni Di Chiro

Work in this section currently focuses on the latest applications of transmission computed tomography and its further development as a noninvasive method for morphologic and functional studies of the nervous system. The section is also very actively involved in emission computed tomography using positron emitting radionuclides (positron emission tomography). Particular emphasis is placed on correlative studies between transmission and emission-computed tomography.

Neuroimmunology Branch—
Dr. Dale E. McFarlin

Research is performed in the following areas: characterization of the immune response to viral agents, such as measles which cause chronic infection in patients with neurologic diseases; study of certain animal models; study of model autoimmune diseases such as experimental allergic encephalomyelitis; assessment of the immune response to components of membranes in the peripheral nervous system and CNS; evaluation of immune function in patients with chronic neurologic disorders of unknown etiology, such as multiple sclerosis and parkinsonism, which may be related to either a persistent infection of the nervous system or immunopathologic mechanisms; assessment of the immune reactivity in human diseases believed to have an autoimmune etiology such as myasthenia gravis; and assessment of new therapeutic agents which alter the immune response.

One medical staff fellow is appointed annually for 2 years. This individual participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as research associates for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Basic Research Laboratories

Laboratory of Central Nervous System Studies—

Dr. D. Carleton Gajdusek

This laboratory is engaged in two studies: (1) The complete medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior, and learning. High incidence and other unusual foci of asthma, parasitic and viral diseases, congenital metabolic defects, atypical patterns of puberty and aging, and behavior syndromes, where isolation or cultural stereotypy may contribute to epidemiologic solutions, are under study. Aspects of learning and socialization in primitive disappearing cultures are documented with the use of still and cinema photography and sound recording. New methods of handling such data are developed. (2) The slow, latent, and temperate virus infections, with particular attention to chronic degenerative neurologic disease and basic virologic and immunologic studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by unconventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie, and mink encephalopathy) that form a new group of microorganisms tentatively called "viruses," although they contain much smaller genetic information and possess very different properties than any other group of viral agents. The biological and molecular characterization of these unconventional viruses is the major focus of the work. Aging of the brain, Alzheimer's, Pick's, Parkinson's and Huntington's diseases, multiple sclerosis, amyotrophic lateral sclerosis, chronic epilepsies, and other diseases are intensively studied in microbiological, immunologic, and biochemical laboratories and clinics and in foci of high incidence throughout the world.

Laboratory of Molecular Genetics—

Dr. Robert A. Lazzarini

Investigates the component molecular events that participate in the replication and expression of the genetic materials of mammalian cells and their viruses. Genetic, biochemical, and recombinant DNA techniques are employed in the study of the replication and transcription of genes and the posttranscriptional modification and translation of ribonucleic acids. These studies are directed toward a full understanding of the delicate interplay between heterologous and complementing genetic elements in chimeric cells and cells persistently or latently infected with viruses.

- Molecular Virology Section—
  Dr. Robert A. Lazzarini

Studies aspects of virus-host interactions at the molecular level. These include viral penetration of host cells, viral replication, and the assembly of progeny particles. Particular attention is focused on the involvement of host factors in the replication of the viral genome and the relationship of these to viral host range, persistency, latency, and cytopathology.

- Recombinant Genetics Section—

Conducts studies of eukaryotic gene expression and genetic complementation in cultured mammalian cells. These studies employ both recombinant DNA and classical biochemical techniques to probe the control of gene transcription, the processing of primary transcripts, and eventual expression of these RNA's as proteins.

Laboratory of Neural Control—

Dr. Robert E. Burke

Fundamental research is conducted on the properties of mammalian nerve cells and on the organization of the mammalian CNS with particular reference to studies of the control of movement. Current experimental studies involve three main areas: 1) the CNS control of spinal cord motoneurons and in turn the control exerted by these cells on the muscle fibers innervated by them, 2) the organization of information-processing systems in the spinal cord, and 3) the activity of motor cortex neurons and of individual peripheral afferents during normal movement in intact animals. Such studies utilize established as well as newly developed techniques for electrophysiologic recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The laboratory has facilities for the development of specialized experimental equipment and novel electrode designs suitable for chronic implantation, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

Laboratory of Neurochemistry—
Dr. Janet V. Passonneau

Research is conducted on molecular events that underlie the normal functioning of the nervous system and derangements that occur in neurologic diseases.

- Section on Cellular Neurochemistry— Dr. Janet V. Passonneau

Section is involved in studies on the metabolism in neural tissues. Emphasis is placed on the microanalytical techniques used to measure metabolites in discrete regions of the brain or in single cells. Projects include the metabolic response of retinal layers to light and dark adaptation, the regional alterations of energy metabolites in ischemia, the role of guanine nucleotides in brain function, and glycogen metabolism in tumor cells of neural origin.

- Section on Enzyme Chemistry— Dr. Wayne Albers

The enzymatic mechanism of active Na+ and K+ transport is investigated. Other current projects involve g-aminobutyric acid metabolism, brain mitochondria, and membrane receptors.

- Section on Neurochemical Pharmacology—Dr. W. David Lust

Section is interested in the role of energy metabolism and of cyclic nucleotides in brain during and after an ischemic episode and in the various stages of experimentally induced seizures *in vivo*. Molecular mechanisms involved in these neurologic disorders are examined in *in vitro* models. Other projects include studies on anticonvulsants and other neurotropic agents.

- Section on Neuronal Development and Regeneration— Dr. Andrew Zalewski

This section is attempting to elucidate the factors involved in nerve fiber regeneration, trophic nerve function, and selectivity and plasticity in the formation of neural connections. A variety of neurohistologic, histochemical transplantation, and immunologic techniques are being used in these studies.

Laboratory of Neuro-Otolaryngology—
Dr. Jorgen Fex

Inner ear neuronal mechanisms are being studied in mammals. The long-range purpose of the project is to study the biochemistry, morphology, pharmacology, and physiology of inner ear neurons and cells and their interactions and to describe the mechanisms of these interactions. A second project concerns the synaptic transmission and neuronal connections of the mammalian cochlear nucleus. A multidisciplinary approach is being used for this project. A major, long-term program of this laboratory is to solve problems concerning hereditary deafness in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models.

Laboratory of Neuropathology and Neuroanatomical Sciences—
Dr. Igor Klatzo

- Section on Functional Neuroanatomy— Dr. Thomas Reese
- Section on Neurocytology— Dr. Milton Brightman
- Section on Experimental Neuropathology— Dr. Jan Cammermeyer
- Section on Cerebrovascular Pathology— Dr. Igor Klatzo
- Section on Cellular Neuropathology— Dr. Henry Webster
- Section on Neurocytobiology— Dr. Maria Spatz

The laboratory recognizes the scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomic sciences. Thus, investigations on mechanisms operative in various neuropathologic conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system. Specific problems under current investigation are cerebral ischemia, hypoxia, brain edema, physiology of the blood-brain barrier, development and pathology of myelin, aspects of vascular permeability and transport mechanisms in the brain, neural membranes, elucidation of junctional complexes, and the source and fate of synaptic vesicles, as well as some of the sensory and motor systems. The main technical approaches include light and electron microscopy; freeze-fracturing; scanning microscopy; histochemistry; radioisotopic, biochemical, and microchemical assays; and tissue culture.

Laboratory of Neurophysiology—
Dr. H. G. Wagner

Research is conducted on the basic properties of nerve cells and on the nervous system. Central neurons and peripheral receptors are studied by biophysical and chemical means with respect to their membrane properties; transduction of external effector stimulus into neural processes; and the selection, generation, and transfer of information through and between neurons.

- Section on Sensory Physiology—
  Drs. T. G. Smith and J. L. Barker

This section investigates the biophysical and pharmacologic properties of membranes and synapses in simple neural systems including tissue-cultured neurons.

- Section on Cell Biology—
  Dr. A. Lasansky

Investigations focus on electrophysiologic function correlated with the microscopic and ultramicroscopic study of morphologic structure in the neural pathways of the vertebrate retina.

- Section on Neuronal Interactions—
  Dr. H. G. Wagner

Attention is on the selection, coding, and transfer of information through and between neurons of the visual system.

Laboratory of Molecular Biology—
Dr. Ernst Freese

Developmental effects of mutations and drugs are examined. They are correlated to hereditary diseases and teratogenic effects.

- Section on Developmental Biology—
  Dr. Ernst Freese

The control of cell differentiation is studied in bacteria, yeast, and mammalian cells by the use of mutations and drugs. The observed effects are examined in terms of metabolism and the control of nucleic acid, enzyme, wall, and membrane synthesis. The molecular mechanisms are analyzed by nucleic acid hybridization, as well as enzyme, membrane, and receptor properties. In addition, mouse embryo cultures are used to measure the development of drug sensitivity and the response to potential teratogens.

Neurological Disorders Program—
Dr. F. J. Brinley, Jr.

The goal of the Neurological Disorders Program is to plan and direct a program of grant and contract support for research and research training on neurologic disorders to ensure maximum utilization of available resources for the attainment of Institute objectives and to collaborate with intramural programs within the Institute and NIH-wide. The program is charged with the study of national priority diseases such as epilepsy; neurologic disorders of the aging; developmental disorders of children and adults; sclerosing and neuromuscular disorders; infectious diseases of the central nervous system; neuroendocrine studies; and learning, behavior, and other sensory disorders. A number of the studies under way are conducted in collaboration with outside institutions. The following programs are conducted by the Neurological Disorders Program of the NINCDS.

Epilepsy Branch—
Dr. Roger J. Porter

This branch develops and coordinates organized and directed research programs on a multi-institutional, geographic, or multidisciplinary basis through its support of five comprehensive programs, each serving a specific geographic area. It develops, conducts, and coordinates collaborative and directed research programs aimed at finding new or improved methods of diagnosis, treatment, and prevention of convulsive disorders. The clinical investigation of new antiepileptic drugs is a major concern. The branch fosters the synthesis, screening, and pharmacologic and metabolic investigation of antiepileptic drugs by collaborative efforts; conducts research on the metabolism of anticonvulsant drugs and the treatment of certain difficult seizure disorders according to rigid protocols within its own facilities; and fosters research in experimental models of epilepsy and improved patient treatment through the use of serum antiepileptic drug determinations.

Developmental Neurology Branch—
Dr. Joseph S. Drage

The branch plans and implements a program of grant- and contract-supported research on the neurologic basis of developmental disorders of children, including the areas of cerebral palsy, autism, mental retardation, learning and behavioral disorders, central nervous system birth defects, heritable muscle and neurologic diseases, and minimal brain dysfunction; assesses the need for research and research training in such areas; determines and recommends program priorities and funding levels for such areas; consults with professional and voluntary health organizations in identifying, developing, and implementing a research program focused on the neurologic basis of development disorders of children; provides for the archival and retrieval system of the Collaborative Perinatal Project data, and promotes the appropriate use of this national data resource commensurate with the goals and mission of the NINCDS.

The Clinical Center

Mortimer B. Lipsett, M.D.,
Director
Jay R. Shapiro, M.D.,
Deputy Director

Blood Bank Department—
Dr. Paul V. Holland

Staff Fellowship

The Blood Bank Department accepts applications for an American Medical Association accredited fellowship program in blood banking and immunohematology. The fellowship assignment can be for 1 or 2 years. Vacancies do not necessarily occur each year. Board certification or eligibility in internal medicine, clinical pathology, or hematology is required.

The program offers training in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. The fellow receives broad experience in all aspects of blood banking, including clinical and laboratory immunohematology, pheresis techniques, donor recruitment, and blood component preparation and therapy. The fellow participates actively in the service and teaching functions of the Blood Bank.

Involvement in a clinical or basic research project is encouraged. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various Institutes. Current programs include investigations into the various agents responsible for posttransfusion hepatitis, the effects of biologic incompatibilities on transfusion and transplantation, and immunologic studies of drug-induced hemolytic anemias, and innovative uses of automated pheresis techniques.

Prospective applicants desiring more information should write to Paul V. Holland, M.D., Chief, Blood Bank Department, Building 10 A, Room 1E33, NIH, Bethesda, MD 20205.

Clinical Pathology Department—

Dr. Ronald Elin

The Clinical Pathology Department offers a broad spectrum of laboratory diagnostic services for intramural patient care for the Institutes. The department is organized into four services: clinical chemistry, hematology, microbiology, and laboratory computer service. The Clinical Chemistry, Hematology, and Laboratory Computer services offer medical staff fellow positions, but not necessarily on a yearly basis.

- Clinical Chemistry—

The Clinical Chemistry Service provides all the chemical diagnostic tests on the patients in the Clinical Center, as well as for outpatient clinics. The senior staff is composed of five individuals with M.D. and/or Ph.D. degrees. Approximately 100,000 tests are performed per month by a technical staff of 42 medical technologists, chemists, technicians, and medical aides. The Clinical Chemistry Service collaborates in clinical research of a chemical nature and conducts extensive research and development in analytic methodology, automation, and computerization. Current interests within the service are the development of radioimmunoassays, adaptation of the calorimeter for laboratory testing, electrophoresis, factors affecting the reference range, instrument evaluation, and automated assay.

A medical staff fellow entering this 2-year program would receive in-depth training in the various aspects of clinical chemistry. The first year of the program would be devoted to a rotation through the clinical chemistry sections—STAT tests, electrophoresis, radioimmunoassay, urinalysis, special chemistry, and microchemistry. In addition, emphasis would be placed on the correlation of laboratory data with the status of patients. The fellow would be encouraged to attend working patient rounds and to handle inquiries to the Clinical Chemistry Service from patient-care physicians. Also, during this first year, the fellow would have the opportunity to develop specific interests in investigative studies. During the second year of the program, the fellow would be encouraged to choose a research project for independent investigation under the supervision of a senior staff member or to participate in an ongoing research project.

Any candidate interested in the Medical Staff Fellow Program should write to Ronald J. Elin, M.D., Ph.D., Chief, Chemistry Service, Clinical Pathology Department, Building 10, Room 2C-407, NIH, Bethesda, MD 20205.

- Hematology

The Hematology Service provides a clinical and research experience in hematology. The service is responsible for the operation of the routine clinical hematology, coagulation, and special hematology laboratories. We have an active clinical and consultative service. The Hematology Service also has a research program directed at clinical and basic problems in hematology. Research of particular interest includes coagulation, thrombosis, platelet disorders, advances in morphologic interpretation of bone marrow material, purification and characterization of coagulation proteins, studies on platelet physiology and pathology, and the study of the role of carbohydrates in coagulation and platelet function. Other research endeavors include the use of immunologic and biochemical markers for hematopathologic diagnoses and the development and testing of new procedures of analytic systems in the hematology laboratory.

The Hematology Service recruits medical staff fellows for a minimum of 2 years. Some fellows will spend at least 6 months doing primarily clinical work with patients in the Clinical Center. During this time, the fellow will also have the opportunity to develop a specific interest in investigative studies. Fellows will be encouraged to choose a problem for investigation which can be pursued with the guidance and supervision available in the Hematology Service, a joint project with an established investigator. Medical staff fellows whose primary interest is laboratory research are assigned to highly qualified physicians to provide an opportunity to improve their backgrounds for careers in basic medical research. During their tenure, these fellows will devote most of their time to laboratory research. The candidate who is chosen will be given an opportunity to choose an area of investigation, and a senior staff member will serve as his or her preceptor.

Any candidate interested in either program should write to Harvey R. Gralnick, M.D., Chief, Hematology Service, Clinical Pathology Department, Building 10, Room 2C-390, NIH, Bethesda, MD 20205.

- Microbiology—

The Microbiology Service provides in-depth training in various aspects of clinical diagnostic microbiology, as well as the opportunity to participate in ongoing developmental research projects. Although the training program is primarily laboratory based, opportunity is considerable for interaction with the Infectious Disease Service and other patient-care physicians. The Microbiology Service is responsible for the isolation and identification of bacterial, mycobacterial, mycologic, and parasitic pathogens in Clinical Center patients. Determinations of antibiotic sensitivity and antibiotic levels are also performed, as well as a variety of clinical serologic procedures. No viral, chlamydial, or rickettsial work is currently performed in our laboratory. Present research activities include the use of computers for the organization and utilization of microbiology laboratory data, the development and assessment of a lysis-filtration and impedance system for blood culturing, the use of laser light-scattering techniques for the determination of antibiotic synergy, and the evaluation of new methodologies for antibiotic sensitivity testing. A variety of clinicopathologic studies is also undertaken or could be initiated under senior staff supervision.

Persons interested in a medical staff fellowship position with the Microbiology Service should contact James D. MacLowry, M.D., Chief, Microbiology Service, Clinical Pathology Department, Building 10, Room 2C-385, NIH, Bethesda, MD 20205.

- Laboratory Computer—

The Laboratory Computer Service provides computer and statistical support for the patient-care and research programs of the Clinical Pathology Department. The service also conducts research on medical laboratory automation, computer-assisted interpretation of clinical laboratory measurements, variation in test results, and methods of quality control. The staff includes pathologists, programmers, and computer operators. In addition to its own minicomputer systems, the service makes extensive use of the NIH IBM 370 and DEC PDP-10 time-sharing computers. Investigators in the service utilize extensive machine-readable files of clinical and laboratory information pertaining to NIH patients.

A medical staff fellow works with the senior staff in applying computer and statistical techniques to problems of laboratory methods. Fellows are encouraged to develop independent or collaborative research projects. In addition, they may participate in teaching conferences of the Clinical Pathology Department.

Interested candidates should write to Thomas L. Lewis, M.D., Chief, Laboratory Computer Service, Clinical Pathology Department, Building 10, Room 2C-306, NIH, Bethesda, MD 20205.

Critical Care Medicine Department—

Dr. Joseph E. Parrillo

The Critical Care Medicine Department is offering 2- to 3-year fellowships in critical care medicine beginning in July 1983. To be eligible, a physician must have completed 3 years of residency in internal medicine, anesthesiology, or general surgery. The fellowship consists of a first year of clinical training in critical care medicine in the intensive care units at the National Institutes of Health and in the medical-surgical intensive care unit at the National Naval Medical Center (Bethesda Naval Hospital). The clinical training provides broad experience in the care of critically ill patients and in a wide variety of procedures necessary to critical care. The second year (and an optional third year for selected fellows) consists of an individually designed program in clinical investigation or basic laboratory research related to critical illnesses. The NIH Fellowship Program is designed to satisfy all the subspecialty Board requirements for critical care medicine. Critical Care Medicine Boards are planned for the first time in 1982.

The fellowship program is designed to provide excellent clinical training in the care of extraordinarily sick patients with multisystem organ dysfunction. The critical care physicians in the NIH ICU have primary responsibility for care of the patient. The critical care physicians work closely with referring physicians and call on multiple consultative services necessary to give full intensive care to these patients. The Critical Care Medicine Department consists of a senior staff that has subspecialty training in cardiology, pulmonary diseases, anesthesiology, infectious diseases, and critical care medicine. The staff performs most of the invasive procedures (Swan Ganz catheterization, cardiac catheterization, bronchoscopy, etc.) themselves in a specially constructed procedure/catheterization laboratory in the ICU. The ICU also has capability for computer processing and analysis, noninvasive (echocardiography, nuclear scanning) cardiac diagnostic studies, and pulmonary function studies.

The fellowship research training is designed to produce independent clinical investigators in the field of critical care medicine. The educational program includes weekly conferences on clinical critical care medicine and seminars regarding ongoing research programs in the department. Each fellow will have a senior staff member guiding the investigations. Ongoing research in the department includes the following: studies of hemodynamics and cardiovascular function in the different forms of shock; the immunopathogenesis of septic shock; capillary leak syndromes; pulmonary functional abnormalities in shock lung; studies of immune cellular function in shock lung, asthma, and other forms of severe pulmonary disease; and critical care of the immunocompromised host.

For further information on the program, please contact Joseph E. Parrillo, M.D., Chief, Critical Care Medicine Department, Building 10, Room 10D48, NIH, Bethesda, MD 20205.

Diagnostic Radiology Department—

Dr. John L. Doppman

Staff radiologists are selected each year from among those applicants who have completed their residencies in diagnostic roentgenology (Board certification not required). Such appointments are made for a period of 2 years, with opportunity for reappointment.

The department is well equipped to provide the routine and special diagnostic radiographic examinations needed by the 50-55,000 patients seen each year. Ultrasound and computed tomography play an increasingly important role in the diagnostic and research activities in the department. The preselection of patients for admission to NIH ensures a challenging and stimulating gamut of diagnostic problems.

Thirteen radiologists comprise the professional staff, and an adequate supporting staff is provided.

Facilities are available for collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

Nuclear Medicine Department—

Dr. A. Eric Jones, Acting Chief

One medical staff fellow is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in nuclear medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved internal medicine, radiology, or clinical pathology is recommended to meet the requirements for certification by the American Board of Nuclear Medicine.

Residency Training

The American Medical Association has approved the department for a 2-year residency training program in nuclear medicine. Qualifications for trainees include at least 2 years of prior training in radiology, pathology, or internal medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital or the Maryland University Hospital.

The department consists of five sections: the Diagnostic Nuclear Medicine Section, the Positron Emission Tomography Section, the Applied Physics Section, the Whole-Body Counter Section, and the Radiopharmacy Section.

The Diagnostic Nuclear Medicine Section provides clinical and investigative service to the physicians of the various Institutes working within the Clinical Center. Rectilinear scanners and gamma cameras are the basic imaging devices. Computers for processing nuclear medicine data are located within the section. Computer experts from the Division of Computer Research and Technology (DCRT) provide professional support for the development of computer-assisted nuclear medicine procedures. The Positron Emission Tomography Section provides positron imaging capability for the study of a broad range of conditions. Currently the emphasis has been on brain glucose metabolism in a variety of disease states and in normal conditions. This section is staffed by physicians, radiochemists, and technicians who have the responsibility of cyclotron preparation of positron-emitting radionuclides, radiochemical production of the agents used in the studies, patient and research imaging, and data production and interpretation. The Applied Physics Section and DCRT personnel work cooperatively in the development of new diagnostic techniques. The Whole-Body Counter Section works closely with the Diagnostic Nuclear Medicine Section and the Radiation Safety Office. It operates three whole-body counters and provides a consultation service to all the Institutes. It is engaged in basic research on trace quantities of radioactivity, personnel monitoring, and a variety of clinical studies. The staffs of the diagnostic nuclear medicine, positron emission tomography, and whole-body counter sections consist of eight physicians, a radiobiologist, two physicists, two radiochemists, an equipment specialist, eight nuclear medical technicians, and three clerks. Departmental professionals are encouraged to interact with members of the various Institutes to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases. The Radiopharmacy Section employs three full-time radiopharmacists, a chemist, a technician, and a clerk to maintain quality control over radiopharmaceuticals used in humans as well as to compound many of the agents used by the Diagnostic Nuclear Medicine Section. This section also provides consultations and support for the use of radionuclides in diagnosis and research.

Division of Computer Research and Technology

Arnold W. Pratt, M.D.,
Director

The Laboratory of Applied Studies, DCRT, offers 2- to 3-year medical staff fellow positions to highly qualified physicians with backgrounds in physical science or engineering (including mathematics through differential equations), 2 years' experience in computer programming, and at least 1 year's clinical experience beyond the M.D. degree.

Laboratory of Applied Studies—
Dr. Eugene K. Harris

This laboratory includes mathematicians, physicians, electronics engineers, statisticians, and computer systems analysts engaged in collaborative studies with other biomedical scientists on modeling of physiologic processes, especially transport, reaction-diffusion, and receptor binding kinetics, and with clinicians on applications of image-processing and statistical analysis to the diagnosis of disease and assessment of treatment, particularly in pulmonary and cardiovascular-renal problems.

The Division in which this laboratory is located supports the world's most powerful, user-oriented biomedical computing facility. Working on one or more specific projects under the preceptorship of a senior investigator, the medical staff fellow will have ready access to and gain familiarity with advanced interactive display devices, graphics terminals, and programming systems for both clinical and basic research.

Part Four

Academic Programs Available to Medical Staff Fellows

Among the academic programs open to an NIH medical staff fellow are: evening courses provided by the Foundation for Advanced Education in the Sciences, Inc., (FAES); formal seminars under the direction of NIH staff; combined clinical staff conferences; formal lectures; and symposia. The "NIH Calendar of Events" lists 25 to 30 programs each week. Other events of interest are held at universities and institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by the Graduate Program of the FAES, established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science. The foundation is an independent organization whose tuition and fees can be paid by a Federal employer. The FAES also operates the NIH bookstore, which supplies textbooks and other reading material for the convenience of NIH staff.

Courses are offered in two semesters, fall and spring. They are offered at the undergraduate and graduate levels under the programs of several departments of instruction: behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages, and general studies. The FAES and the Clinical Center sponsor Board review courses in medicine and pediatrics. Subspecialty courses are offered for Board review in endocrinology, hematology, and oncology. Further inquiries regarding the Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education in the Sciences, Inc., National Institutes of Health, Bethesda, MD 20205.

Seminars

An NIH program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent investigators and gives them the additional opportunity to master selected topics not adequately covered during college or graduate schooling. These seminars are now administered by the FAES, in conjunction with the evening courses. The program accommodates medical staff fellows involved in clinical or basic research and other properly qualified persons.

A number of tutorial seminars are generally made available each academic year in each of the following categories: biochemistry and genetics, cell biology, immunology, and physiology.

Weekly seminars run from September through January and from February through June. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of an expert in the field. In preparation for these, the medical staff fellow does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate Institutes engaged in clinical research, the Clinical Center sponsors at least one monthly combined clinical staff conference for 8 months of the year. Each conference is conducted by one of the Institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff and serve to keep individual investigators abreast of current emphasis in all clinical research.

Topics Presented in the 1981-82 Series Were:

September 17, 1981	Dr. Thomas Waldmann	Ataxia Telangiectasia
November 12, 1981	Dr. Michael Frank	The Reticuloendothelial System in Man
December 17, 1981	Dr. Theodore Nash	Schistosomiasis in Man
January 21, 1982	Dr. Jay Hoofnagle	Chronic Type B Hepatitis
February 18, 1982	Dr. Michael Ebert	Applications of 2-Dimensional Protein Electrophoresis in Clinical Research
April 15, 1982	Dr. John Minna	Biology and the Treatment of Lung Cancer
May 27, 1982	Dr. Anthony Fauci	Immunoregulation in Normal and Disease States
June 10, 1982	Dr. E. Anthony Jones	Primary Biliary Cirrhosis
July 22, 1982	Dr. Ronald Crystal	Oxidant Injury to the Lungs

Several formal lectures are presented annually. **The National Institutes of Health Lecture Series** was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the scientific directors of the Institutes. Dr. Joseph Goldstein of the University of Texas Southwestern Medical School gave the most recent NIH lecture in December 1981 on "Cell Surface Receptors for Plasma Lipoproteins: Implications for Biology and Medicine."

The **R. E. Dyer Lectureship** was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942-50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science. Dr. Matthew D. Scharff of the Albert Einstein College of Medicine presented the 1981 Dyer lecture on "Somatic Variation in Immunoglobulin Production by Mouse Myeloma Cells." Among other distinguished speakers have been two Nobelists, Dr. Howard M. Temin, who spoke on "The Replication and Possible

Origin of RNA Viruses with a DNA Polymerase" and Dr. D. Carleton Gajdusek, who discussed his work on "Kuru."

The **G. Burroughs Mider Lectureship** was established in 1968 by the scientific directors to honor Dr. Mider for his distinguished service to NIH. On advice of the scientific directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Recent Mider Lectures:

1981	Dr. Louis Sokoloff	Metabolic Mapping of Local Functional Activity in the Central Nervous System
1980	Dr. Thomas Waldmann	The Control of the Immune Response Regulatory Cellular Interactions and the Control of Lymphocyte Differentiation
1979	Dr. Martha Vaughan	Regulation of Cyclic Nucleotide Metabolism
1978	Dr. Jesse Roth	Receptor Disorders in Man
1977	Dr. Philip Leder	A Close and Surprising Look at the Mammalian Genome
1977	Dr. Maxine F. Singer	Monkey Business: Sequences in the Monkey Genome and Their Interaction with Simian Virus 40 DNA
1975	Dr. Karl A. Piez	Collagen: Its Chemistry, Structure and Function
1974	Dr. Elizabeth F. Neufeld	Inherited Lysosomal Disorders Studies in Cell Culture

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These, and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the new Uniformed Services University of the Health Services at the National Naval Medical Center, offer exceptional educational opportunities. Some medical staff fellows augment their experience at NIH with studies at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located on the first floor of the Clinical Center) is an open-stack, self-service library with a collection of some 230,000 volumes of medical and scientific books and journals. Some 5,000 books and 3,800 journal subscriptions are received annually. Organizationally under the Division of Research Services, the NIH Library is an integral part of the research needs of the NIH staff. Its major subject areas include medicine, health sciences, chemistry, physiology, biology, physics and the peripheral areas of economics, education, legislation, and social sciences. A full range of services is provided NIH employees, including library copy service, manual and on-line bibliographic service, interlibrary loan, advisory consultation for literature needs and a translating service.

The National Library of Medicine (NLM) is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 2 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service. Access to the library's computerized data base of journal references (MEDLINE) is available both at NLM and at the NIH library.

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NIH Publication No. 82-
Revised April 1

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November 15, 1983	Deadline for receipt of completed NIH Medical Staff Fellow applications
January 9-20, 1984	Interview period
February 6, 1984	Notification to all candidates

Applications may be obtained from:

The NIH Medical Staff Fellowship
Program
Building 10, Room 2N220A
National Institutes of Health
Bethesda, MD 20205
Tel: 301-496-2427

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Foreword

The National Institutes of Health and the Warren Grant Magnuson Clinical Center, the research hospital for the Institutes, are international centers for biomedical research and clinical investigation. The Clinical Center and the other intramural research facilities in Bethesda have provided research and training opportunities for thousands of foreign scientists and physicians and for an even greater number of research scientists and clinical investigators in this country.

The Clinical Center has 540 beds to which patients are admitted for participation in research protocols. The protocols are directed towards understanding disease as well as towards diagnosis and treatment. The proximity of the wards to the 1,200 research laboratories ensures continuing collaboration between clinical and laboratory scientists. Within this scientific community there are unique opportunities to acquire the skills necessary for biomedical research. This catalog describes the opportunities open to physicians and dentists in the Medical Staff Fellowship Program at the NIH.

Michael H. Ebert, M.D.
Acting Director

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Part One

General Description of Medical Staff Fellowships and Other Opportunities

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The Warren Grant Magnuson Clinical Center

Michael H. Ebert, M.D.
Acting Director

The Warren Grant Magnuson Clinical Center is a modern laboratory hospital facility shared by the 11 Institutes that conduct combined laboratory and clinical study programs. This 540-bed research hospital is located on a 300-acre campus at the National Institutes of Health (NIH) in Bethesda, Maryland.

NIH is the largest biomedical research organization in the world. Approximately 2,600 staff members have doctoral degrees, including almost 1,000 with M.D. degrees, more than 1,500 with Ph.D. degrees, and about 40 with D.D.S. and 50 with D.V.M. degrees. A significant number have more than one doctorate.

Three Nobel laureates work on the campus: Drs. D. Carleton Gajdusek, Julius Axelrod, and Marshall W. Nirenberg. Dr. Gajdusek received the award in 1976 for his work in proving that kuru—a fatal disease affecting the nervous system—is a transmissible slow virus infection.

In 1970, Dr. Axelrod was cited for discoveries concerning transmitter substances in nerve terminals and mechanisms for their storage, release, and deactivation. Dr. Nirenberg was honored in 1968 for his work on the translation of the genetic code and its function in protein synthesis.

Three other scientists received the Nobel prize for work done while at NIH. In 1976, Dr. Baruch Blumberg was honored for his discovery of the "Australia antigen," a marker of hepatitis B. The prize was given to Dr. Anfinsen in 1972 for his studies of ribonuclease, particularly the relationship between amino acid sequences and the conformation of enzyme molecules. Dr. Arthur Kornberg received the award in 1959 for his research on the mechanisms in the biological synthesis of DNA and RNA.

With the help of a staff of almost 3,000 technical personnel, NIH scientists are involved in some 2,500 research projects which result in more than 5,000 published scientific articles each year. The budget for this intramural research effort is approximately $486 million.

The 14-story Clinical Center represents an important resource for training in medical research. The hospital provides a setting in which a young physician can participate in medical care, acquire new clinical skills, and carry out research in a laboratory conveniently located a few steps from the patient's room. The center is designed to bring scientists working in laboratories into close proximity with clinicians caring for patients so that bench investigators and physi-

cians may collaborate on problem diseases.

The primary mission of the Clinical Center is to provide a specialized form of hospital care necessary for Institute studies. To accomplish this goal, the Clinical Center has developed patient care programs and related technical support systems which stand at the fore of modern health care.

The Nuclear Medicine Department provides whole-body scanning and diagnostic imaging through the use of radioactive pharmaceuticals. Positron emission tomography and radionuclide cineangiography are among the imaging techniques under study. The Diagnostic Radiology Department has a full complement of radiological equipment, including CAT scanners and ultrasonic scanners. Nuclear magnetic resonance and digital fluorographic devices are among those the department plans to acquire and evaluate. The superbly equipped clinical pathology laboratories provide optimum support to physicians and their patients. The Blood Bank provides blood products for the patients, teaches blood banking and immunohematology, and conducts research.

Numerous opportunities are available for medical staff fellows to participate in the use and development of modern medical computer systems, medical instrumentation and electronics. These systems are used for patient care, for clinical and basic research, and for the education of staff fellows in the use of computers in medicine.

A large, computer-based Medical Information and Communication System is used in support of patient care in the Clinical Center and the adjoining Ambulatory Care Research Facility. Two hundred display terminals and 85 printers are located on the Clinical Center nursing units and in-service department areas to permit rapid retrieval of patient information and processing of medical orders. This system is used by physicians, nurses, and other medical professionals as part of their daily patient care activities. In addition, information obtained during the patient care process is available through the central NIH computer facility for retrieval and research analysis.

The Clinical Center admits approximately 7,700 patients yearly. In addition, the outpatient clinics service over 100,000 patient visits annually.

A newly completed 13-story Ambulatory Care Research Facility (ACRF), adjacent to the original Clinical Center structure, is designed to expand and strengthen the combined laboratory and patient care programs of the Clinical Center. It is estimated that the new wing will double the Clinical Center's outpatient capacity. The facility will provide an optimum environment to care for and study outpatients, yet it will retain the same proximity between clinical and laboratory scientists that has successfully promoted medical inquiry in the existing Clinical Center.

The Clinical Center appoints medical staff fellows for the Departments of Clinical Pathology, Critical Care Medicine, Nuclear Medicine, and the Blood Bank. These programs are described in part three.

The Medical Staff Fellowship Program

Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists through appointments as medical staff fellows at the National Institutes of Health. These positions encompass most medical specialties and basic science disciplines.

Appointments to the Medical Staff Fellowship Program (formerly the Associate Training Program and encompassing what used to be designated clinical, research, and staff associate positions) are based on professional attainment, research interest, and ability. The NIH seeks outstanding candidates and selection is made without regard to race, sex, geographical location, or university affiliation. Candidates may be selected because of demonstrated excellence in research or in a clinical discipline. Selections are made through a matching process explained in part two.

Each medical staff fellow participates in a research program under the direction of a preceptor. Preceptors, drawn from a large number of skilled investigators, serve to enrich each staff fellow's experience. Because of the unique blending of clinical and nonclinical scientists, the staff fellow is in daily contact with scholars representing a variety of research interests.

The NIH offers many educational opportunities ranging from tutorials to sponsored lectureships. Postgraduate instruction, sponsored by the Clinical Center or the graduate program of the Foundation for Advanced Education in the Sciences, Inc., is available on a broad range of topics, including mathematics, languages, laboratory skills, and clinical reviews (see part four).

The NIH affords the medical staff fellow the opportunity to participate in clinical and laboratory research. Clinical activities are carried out near laboratory facilities and are under the immediate supervision of senior investigators. This proximity to patients and to collaborating scientists from many biological disciplines has created a superb environment for learning and performance of clinical research.

Some fellows devote most of their time to laboratory research in a biomedical science. The preceptor is responsible for training in research methods and design, and for guidance in the conduct of specific research undertakings and in the interpretation of results. One of the goals of the program is to select research problems which will enable the staff fellow to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The medical staff fellow position also provides opportunities for those highly qualified candidates who could contribute significantly to research areas not specifically designated in the research or clinical categories. In these cases, the staff fellow may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he or she works. Research experience may be supplemented by attending formal evening study courses, lectures by guest speakers and a variety of medical seminars.

The Dental Staff Fellow

Like medical staff fellows, the dental staff fellow may participate in laboratory and clinical research, and enhance professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the fellowship, there is full opportunity for a fellow to become familiar with all ongoing research programs relevant to dentistry; affiliate with one or more preceptors to participate in a mutually acceptable area of investigation; and extend scientific background through rounds, conferences, seminars, and formalized course work.

The Medical Staff Fellow in Pharmacology (Pharmacology Research Associate Program)

Staff fellows in this program, sponsored by the National Institute of General Medical Sciences, spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those committed to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

Staff Physicians

Some physicians, already qualified in a specialty, are not appointed as medical staff fellows but as staff physicians. Initial appointments are temporary and usually for 2 years, but some staff physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part-time in research.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to medical students. For 1983-84, the staffs of several Institutes are collaborating to supply an in-depth exposure to 15 clinical subspecialties: anesthesiology, clinical dental care, critical care medicine, computers in clinical medicine, endocrinology and metabolism, genetics, geriatrics, immunology, medical-surgical neurology, neurobiology, nuclear medicine, oncology-hematology, psychopharmacology, pediatric psychopharmacology, and surgical oncology.

The essence of this educational experience is close association between the student, staff fellows, and physician-scientists in several of the Institutes.

Students are assigned patients for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with interests in fields other than those listed above are sometimes arranged through communication between an NIH staff member and a faculty sponsor of the students.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Clinical Electives Program Office
Building 10, Room 2N220A
National Institutes of Health
Bethesda, MD 20205

Approved Training Programs

Residency training programs approved by the Accrediting Council on Graduate Medical Education are offered in anatomical pathology and nuclear medicine as are fellowships for advanced subspecialty training in blood banking, and clinical pathology, including clinical chemistry, hematology, and microbiology, and the laboratory computer service.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Lance A. Liotta, M.D., Ph.D.
Chief, Laboratory of Pathology
Building 10, Room 2A33
National Institutes of Health
Bethesda, MD 20205

Steven M. Larson, M.D.
Chief
Nuclear Medicine Department
Building 10, Room 1C401
National Institutes of Health
Bethesda, MD 20205

Board Certification: The first year of the clinical fellowship in the National Heart, Lung, and Blood Institute is accredited as a third year of training in internal medicine by the American Board of Internal Medicine. The 3-year medical staff fellowship has been accepted for training by the subspecialty board in Infectious Diseases and the conjoint Board of Allergy and Immunology.

Credit towards board certification is offered in the following specialties and subspecialties:

Allergy/infectious diseases
Blood banking
Cardiology
Clinical chemistry
Critical care medicine
Dermatology
Endocrinology
Hematology
Gastroenterology
Genetics
Internal medicine (NHLBI only)
Medical oncology
Microbiology
Neurology
Pediatric endocrinology
Pediatric genetics
Pediatric hematology/oncology
Pediatrics
Psychiatry
Reproductive endocrinology
  (obstetrics and gynecology)
Rheumatology

The amount of credit earned depends on the training completed and the acceptability of such to the individual board. Candidates are advised to consult the appropriate Institute and specific subspecialty board for additional information.

Endocrinology Fellowship Program

The NIH Endocrinology Fellowship Program is an interinstitute program which involves most of the clinical branches working in this field on the campus at Bethesda. It is devised for physicians who seek a broad experience in both fundamental research and clinical experience in endocrinology. Fellows are selected for a period of 2 or 3 years which includes approximately 1 year of clinical activity among several endocrinology branches of the NIH. During this clinical period, fellows function as primary care physicians for the 70-bed endocrinology inpatient services, serve as consultants for other services of the 540-bed Clinical Center as well as for other local hospitals, and participate in outpatient work, rounds, and seminars. The remainder of the time is spent primarily in laboratory investigation under the direction of a senior investigator in one of the endocrinology branches. During this research period opportunity exists for continuing outpatient work and participation in clinical conferences. No position will be offered for a single year.

Medical staff fellows selected by any of the three endocrinology branches of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (Clinical Endocrinology, Diabetes, or Metabolic Diseases) as well as the Developmental Endocrinology Branch of the National Institute of Child Health and Human Development automatically participate in the interinstitute program. Medical staff fellows from other branches may participate only under special circumstances. The National Heart, Lung, and Blood Institute also participates in the interinstitute program.

Lectures and Courses

The NIH campus provides a stimulating intellectual environment for continuing education, including multiple clinical and basic science conferences and journal clubs, as well as tutorial seminars and courses spanning many disciplines. The endocrinology fellowship program sponsors formal endocrinology seminars and lecture series covering the field broadly and in detail. The Computer Science Division and Radiation Safety Branch provide detailed practical work and study in these fields. The latter branch gives an intensive course in the use of radionuclides, enabling graduates to apply for their own radioisotope license after completion of the fellowship.

Medical Student Program

Students selected from various medical schools throughout the country participate in endocrinology courses offered three times yearly. Fellows work in close association with the students and supervise their patient care activities. These and other teaching functions help develop the fellows' skills as educators in preparation for later academic careers.

Internal Medicine and Endocrinology Board Examinations

Studies in the Clinical Center relate to all areas of internal medicine, and fellows are encouraged to develop their general clinical skills. Completion of the fellowship program satisfies requirements for the Endocrinology Subspecialty Board Examination. Because of recent changes in the requirements for the Certifying Examination of Internal Medicine, applicants are encouraged to review their residency training plans directly with the Board.

Prospective applicants who would like further information on the program should write Bruce D. Weintraub, M.D., Building 10, Room 8N315, National Institutes of Health, Bethesda, MD 20205.

Medical Genetics Program

The NIH Interinstitute Medical Genetics Program is a cooperative undertaking involving several clinical branches and research laboratories in various institutes on the Bethesda campus. It is a program of 2-, or in rare cases, 3-years' duration for physicians seeking broad exposure to both research and clinical experience in human genetics. The training is also designed to fulfill all requirements proposed by the American Board of Medical Genetics for fellowships leading to eligibility for Board certification.

The fellowship includes clinical activities and laboratory or clinical investigations under the direction of a senior scientist. Fellows are responsible for outpatients seen at the weekly NIH Genetics Clinic. They also serve as genetics consultants in the 500-bed Clinical Center and participate in weekly patient conferences and ward rounds. Further opportunities to become familiar with the spectrum of patients with genetic disease are provided by optional attendance at genetics clinics at collaborating institutions including the Johns Hopkins Hospital in Baltimore and the Prenatal Diagnosis Unit at George Washington University Hospital in Washington, D.C.

Entrance into the Medical Genetics Program is through either of two routes: fellows may be accepted directly into it, and then later choose a laboratory in which to do research; or, alternatively, fellows may be selected by a research branch or laboratory in one of the participating institutes and then apply for acceptance into the Medical Genetics Program. Candidates choosing the second route must indicate their interest in the Medical Genetics Program on the medical staff fellowship application form; they will then be interviewed by the program's steering committee as well as by scientists from the research branches to which they have applied.

Fellows in the Medical Genetics Program pursue research chosen from many types of investigations related to genetic diseases; descriptions of the diverse interests of participating scientists are provided in a brochure which will be supplied to fellowship applicants. The aim of this program is to provide fellows with research experiences of the highest caliber and to prepare them for careers as independent investigators in medical genetics.

The fellowship program also includes a seminar series in medical genetics in which invited speakers discuss research and clinical topics of current interest, and a journal club. Other opportunities for continuing education (clinical and basic science conferences, tutorial seminars and postgraduate courses) are plentiful on the NIH campus. The fellowship program also sponsors a yearly 8-week elective in medical genetics for senior students from medical schools around the country; fellows assist in didactic lecture-demonstrations on the approach to patients with genetic diseases and in supervision of students in patient-related activities. These and other teaching opportunities develop the fellow's skills as educators in preparation for future academic careers.

Applications for the fellowship program should be directed to the Medical Staff Fellowship Office (see p. 9). Further information may be obtained by telephon from Drs. John J. Mulvihill or Dilys M. Parry at (301) 496-4947.

Part Two

Applying for a Medical Staff Fellowship

About 125 medical staff fellows are appointed annually to positions emphasizing clinical or basic research. Fellows are employed through the Public Health Service (PHS) in special civil service appointments, but not in the Commissioned Corps of the PHS.

Minimum eligibility requirements for most medical staff fellowships is completion of 2 years of graduate medical training before entrance on duty. Application should be made between 1 and 2 years before desired date of appointment.

To be considered for a medical staff fellowship, completed application forms must be received in the NIH Medical Staff Fellowship Office, Building 10, Room 2N220A, National Institutes of Health, Bethesda, MD 20205, by November 15, 1983.

Participants in the National Health Service Corps Scholarship Program are not eligible for consideration until after they have served obligated pay-back years in NHSC-designated areas of medical need.

To be eligible for a PHS appointment as a medical staff fellow (not in the Commissioned Corps), a candidate must meet the following requirements:

- Be a United States citizen or a permanent U.S. resident.
- Meet the medical fitness standards.
- Be a graduate of an accredited medical, osteopathic, or dental school.
- Satisfactorily complete an internship (PG1) approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)
- Foreign medical graduates—foreign nationals or American citizens who have received their medical degree from a medical school outside the United States (including Puerto Rico) and Canada and that is listed in the World Health Organization's *World Directory of Medical Schools*—must be certified by the Educational Commission for Foreign Medical Graduates (ECFMG). Passage of the Visa Qualifying Examination (VQE) satisfies the medical science examination requirement for ECFMG certification. Beginning in 1984, a new Foreign Medical Graduate Examination in the Medical Sciences will replace both the present ECFMG medicine examination and the VQE.

Employment Benefits for Medical Staff Fellows

Medical staff fellows are entitled to the following benefits which are comparable to those offered to Civil Service employees: partial subsidy for health insurance and group life insurance, retirement benefits, occupational medical emergency service at NIH, compensation for injury, 13 working days of annual leave per year and the same amount of sick leave, and training at Government expense. Medical staff fellows will be paid for entry-on-duty travel to NIH and shipment of household goods. Return travel and shipping will also be paid to fellows who leave after completion of their initial assignment.

Method of Selection—
Matching Program

Selections for medical staff fellow appointments are made through a matching process in which the candidate's preferences are matched with the Institute's preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Checklist." After reading part three of this catalog, the candidate should check off on these sheets the areas in which he or she is interested. There is no limit to the number of interest areas which may be checked. The application will be sent to all laboratories and branches which the candidate has checked.

After thorough review by the Institutes of all applications, a limited number of candidates will be selected for personal interviews after which the candidate submits his or her confidential preference list. *Applicants should only list programs in which they have an interest and would accept if chosen. In a highly competitive selection system, failure to accept a position after the "match" compromises another candidate's opportunities.*

The NIH Medical Staff Fellowship Office will set up the interview and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

Part Three

Program Areas for Which Candidates May Apply

Each of the major NIH components has prepared a description of its program areas for which medical staff fellows may seek appointment. These descriptions are meant to anticipate many of the questions applicants may have in selecting program areas for which they wish to be considered. *It should be noted that a candidate is not limited as to the number of kinds of positions for which he or she may apply.*

National Cancer Institute

Vincent T. DeVita, Jr., M.D.,
Director and Clinical Director

Division of Cancer Biology and Diagnosis

—Alan S. Rabson, M.D., Director

The Division of Cancer Biology and Diagnosis is broadly concerned with biochemical, genetic, physiologic, immunologic, and metabolic derangements that predispose organisms to neoplasia and that result from neoplasia. Within this area, a wide variety of research interests are pursued which involve basic questions of immunology, virology, molecular biology, and biochemistry of normal and pathologic states.

The Division is composed of several branches and laboratories, each under the direction of a branch or laboratory chief. Medical staff fellow positions are available in many of these areas and fellows work exclusively with the branch or laboratory in which they are accepted. All fellows have a unique opportunity to become experienced scientists in their fields of interest and thereby initiate a career in academic medicine and research.

Appointments in Clinical Research

Clinical positions are available for medical staff fellows in the Metabolism Branch, Immunology Branch, Dermatology Branch, and the Laboratory of Pathology. Fellows participate in patient care directly related to the research interests of the branch and engage in general research under the direction of individual scientists. The scope and orientation of each of these positions depends, of course, on that of the particular branch or laboratory.

Appointments in Laboratory Research

Nonclinical positions are available in the following laboratories: Biochemistry, Pathophysiology, Molecular Biology, Immunobiology, Cell Biology, Genetics, Mathematical Biology, and Tumor Immunology and Biology.

In general, fellows are engaged in original research under guidance of individual investigators who act as preceptors for the fellows.

Clinical Research Branches

Dermatology Branch—
Stephen I. Katz, M.D., Ph.D.

The Dermatology Branch studies the growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic, neoplastic, and inflammatory states; protein synthesis by epithelium, especially of tonofilaments, keratohyalin, and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; physiology of lymphoreticular cells and lymphokine formation; and the biological activity of oncogenic viruses.

Also studied are experimental allergic contact dermatitis; scanning and transmission microscopy of normal and diseased skin and other tissues; scanning microscopy of the cell-surface structure in relation to the mitotic cycle and motility; genodermatoses; biochemical and ultrastructural aspects of melanogenesis in normal and melanoma tissue; biochemistry and keratinization; xeroderma pigmentosum, an inherited disease of sun sensitivity, and multiple cutaneous cancer with abnormal DNA repair; clinical, chemical, and ultrastructural effects of vitamin A on skin; the oncogenic potential of tumor viruses; the development of therapy of epithelial cancers, skin lymphomas, and keratinizing diseases of the skin.

Immunology Branch—
David H. Sachs, M.D.
Senior Investigators
- Howard B. Dickler, M.D.
  Ronald E. Gress, M.D.
  Maryanna P. Henkart, Ph.D.
  Pierre A. Henkart, Ph.D.
  David M. Segal, Ph.D.
  J. Stephen Shaw, M.D.
  Gene M. Shearer, Ph.D.
  Alfred Singer, M.D.
  Dinah S. Singer, Ph.D.
  John R. Wunderlich, M.D.
- Immunotherapy Section—
  Richard J. Hodes, M.D.
- Transplantation Biology Section—
  David H. Sachs, M.D.
  Jeffrey A. Bluestone, M.D.

The Immunology Branch is concerned with the chemistry, genetics, biology, and clinical significance of immunity. Cellular immunity, transplantation immunity, and the nature of mammalian cell surfaces are the fundamental areas developed within the branch. Information derived from each of these areas is applied to studies of the relationship between the immune system and neoplastic cells in experimental animals and man.

Biochemical, biophysical, genetic, biological, and clinical investigative techniques are utilized in these studies.

Cellular Immunity—The cell-mediated immune responses of laboratory animals and human beings are being investigated. The responses studied *in vitro* include cellular proliferation, cell-mediated cytotoxicity, and antibody production. Immune mechanisms which could be relevant for autologous neoplastic cell rejection are investigated. Immunity to chemically modified autologous cell-surface antigens, to autologous cells infected with influenza virus, immunity of F_1 hybrid cells to parental antigens, and cellular immune responses to cultured/syngeneic tumor cell lines represent the models under study. The role played by the major histocompatibility complex (MHC) both with respect to the MHC-product-associated immunogenic complexes found and to MHC as well as non-MHC immune response genes controlling reactivity to these immunogenic complexes is under investigation.

The immunosuppressive events associated with and leading to the newly discovered acquired immune deficiency syndrome (AIDS) are being investigated by studying by the *in vivo* immune potential of human peripheral blood leukocytes, and by using *in vitro* and *in vivo* murine immune models. Particular emphasis is being placed on the possible synergistic effects of virus, exposure of the lymphoid system to sperm, and the suppressive and stimulatory signals associated with *in vivo* allogeneic lymphocyte reactions.

The nature of regulatory influences on the cell-mediated immune response to transplantation antigens is being investigated. Both synergizing and suppressive lymphoid subpopulations have been characterized in *in vitro* systems. Further work is being directed at the mechanisms of such regulatory influences, the role and expression of products of the *I* region of the MHC in these events, and the potential relevance to *in vivo* phenomena including transplantation and tumor immunity.

The mechanisms by which immune, as well as nonimmune lymphoid cells kill specific target cells are also under investigation. *In vitro* studies are utilized to evaluate direct killing of mammalian cells by "killer" lymphocytes, and attempts are made to relate findings to *in vivo* functions of cytotoxic lymphoid cell populations. Studies characterizing the nature of antibody mediated, lymphocyte-dependent target cell killing are in progress.

Studies with monoclonal antibodies have provided evidence that this receptor plays a key role in functional activation of B-lymphocytes.

The receptors for immune complexes (Fc receptors) on different immunocompetent cell populations are being characterized by a variety of methods. The interactions of these receptors to antigens determined by the immune response gene region of the MHC (Ia antigens), surface IgM and IgD, as well as to other cell-surface molecules are being investigated. The role of this receptor and these interactions in the immune response and the regulatory role of antibody are currently being studied.

Humoral Immunity—A number of *in vitro* assays have been developed and characterized in the mouse including: (a) primary and secondary antibody plaque-forming cell assays, T-cell proliferation assays, and antibody-secretion-enzyme linked immunoassay for use with a variety of antigens, including those under genetic control; and (b) T-lymphocyte and accessory cell independent B-cell responses to antibodies specific for antigen receptors plus T-cell replacing factor(s). These assays are being used (1) to evaluate the cellular level of expression of immune response genes and the mode of action of such genes, (2) to evaluate the role of cell-surface antigens determined by the *I* region of the H-2 complex and the role of subpopulations of cells bearing these antigens, (3) to characterize the nature and mechanism of action of antigen-specific helper and suppressor factors, (4) to evaluate the immunologic role of idiotype-bearing molecules of both T- and B-lymphocyte origin, and (5) to use purified factors and monoclonal antibodies to characterize the cell-surface molecules responsible for triggering and/or regulation of responses. Antibodies to idiotypic specificities of antibodies, the levels of which are regulated by immune-response genes, have been shown to directly activate both helper T-lymphocytes and B-lymphocytes.

Transplantation Immunity—Antibodies against histocompatibility antigens and tumor antigens are used as reagents for determining the nature of these antigens and manipulating the immune response against them. Studies utilize inbred rats and mice and congenic mice. Strains of miniature swine have been developed to provide large quantities of materials for chemical characterization of surface antigens and as a model for organ transplantation studies.

Antibodies with specificities directed against transplantation antigens are being examined for chemical and immunologic individuality. Mouse lymphocyte alloantigens determined by genes in the *Ir* region (Ia antigens) are being studied serologically and functionally. Hybridomas producing monoclonal anti-H-2 and anti-Ia antibodies are being produced and characterized. Receptors of these antibodies are being examined for unique and for shared idiotypes.

Anti-idiotypic antibodies are being used to modify immune responses to transplantation antigens.

Human allogeneic T-cell responses are being used as a probe to define new antigens in the HLA regions. New gene products already defined by this approach are being studied for their relevance in regulating human immune responses and for association with human diseases.

New approaches to bone marrow transplantation are being explored. These include the use of monoclonal antibodies to eliminate GVH-producing donor cells. Experiments in animal models and at the clinical level are anticipated.

Cell Membranes—The chemistry of lymphoid cell membranes is being investigated in an effort to characterize the molecular makeup of surface components as well as to identify and study specific functional receptors. Simple defined membrane systems are being designed to model immunologic phenomena such as cell-mediated cytotoxicity and patching and capping of surface antigens. The nature of the membrane lesion generated by different types of cell-mediated killing (T-cells, K-cells, etc.) is under investigation.

Immunochemistry—The structural and biological consequences of antigen-antibody interactions are being examined by using affinity cross-linked oligomers of IgG antibodies as models for naturally occurring immune complexes. The oligomers are being used to characterize immunoglobulin receptors on various cell types, to assess the effects of antibody polyvalency on cell binding, and to study the physiological consequences of the interactions of cross-linked immunoglobulins with cells. Affinity cross-linked oligomers are also being used to study the interaction of complement with IgG antibodies.

Tumor Immunology—Cellular immune mechanisms of tumor-bearing animals and patients with a variety of malignancies are studied, and attempts are made to modify reactions so as to improve tumor cell kill. Specific assays are established to determine the presence of humoral and cell-mediated responses of hosts to tumors.

Alternative assays are being tested for use in detecting early events in the recognition of malignant cells by host immune lymphoid cells. By means of such assays, attempts will be made to define at a structural level the characteristics of tumor cell-surface antigens which render these cells either susceptible or resistant to immune destruction in the tumor-bearing hosts.

Immunotherapy of tumors is approached both in animal models and patients using nonspecific and specific stimulation of the immune system. A clinical study is now in progress to evaluate the effectiveness of adjuvant therapy in preventing recurrence of malignant melanoma in patients who have been rendered clinically free of disease but who have poor prognosis in the absence of therapy. Comparison is being made between adjuvant chemotherapy with methyl-CCNU and immunotherapy with either BCG alone or BCG plus a vaccine of neuraminidase-treated allogeneic melanoma cells. In addition to monitoring the clinical status of these patients, laboratory tests are carried out to study the immune responses induced by the therapy.

Molecular Immunology—Investigation of the molecular mechanisms that regulate the expression and synthesis of histocompatibility antigens has been recently initiated. A genomic DNA segment containing a functional MHC gene has been isolated. The regulation of expression at the MHC gene in a heterologous cell and the DNA sequence organization of the entire genomic segment are currently under investigation.

Metabolism Branch—
Thomas A. Waldmann, M.D.
- Cellular Immunology Section—
  R. Michael Blaese, M.D.
- Endocrine Section—
  James M. Phang, M.D.

The Metabolism Branch is broadly concerned with clinical and laboratory studies that focus on the immunologic, endocrinologic, and metabolic bases of disease occurring in patients with neoplasia.

Immunologic interests encompass studies of immune regulation, including factors controlling helper and suppressor T-cell function in immunodeficiency states (hypogammaglobulinemia, IgA deficiency, Wiskott-Aldrich syndrome, and ataxia telangiectasia), in leukemias of T-cells, as well as in animal models of disordered immunity. Other areas of immunologic interest include studies using recombinant DNA technology to examine the genes controlling immunoglobulin synthesis and their organization and studies of the genetic basis of immunity, including the relationship between HLA antigens and disease and genetic factors controlling the response to complex chemically defined proteins; studies of cytotoxic effector mechanisms and the role of macrophages in the afferent and efferent limb of the immune response; studies of gastrointestinal (GI) tract immunology, including the investigations of intestinal lymphangiectasia, GI allergy, and GI abnormalities associated with immunodeficiency; studies of patients with lymphoproliferative neoplasms including multiple myeloma and chronic lymphocytic leukemia; and T-cell leukemias including Sézary syndrome, with the aim of defining the T-cells with retained immunologic functions. The structure and functions of the T-cell receptor for T-cell growth factor are being analyzed using a monoclonal antibody to this receptor that was prepared by this branch. The isolation and characterization of immunoregulatory biological modifiers is being performed using cloned T-cell lines and T-T cell hybridoma technology.

Endocrine interests include biochemical studies of amino acid metabolism related to collagen synthesis and gluconeogenesis (studies of regulation of enzymes in the collagen synthetic pathway and the proline degradative pathway). These are related to studies of patients with disorders of metabolic bone disease, diabetes mellitus, and amino-acidopathies. Studies of growth hormone, somatomedin, and other growth peptides are related to studies of patients with growth disorders.

Basic Research Laboratories

Laboratory of Biochemistry—
Maxine Singer, Ph.D.

The emphasis of the work in the laboratory is on the relation between structure and function in biological systems and on the regulation of cellular processes. The research involves prokaryotes and a range of eukaryote systems selected because of their potential for yielding important information on cellular structure, function, regulation, development, and differentiation. The study of regulation encompasses regulation of gene expression, regulation by interaction of macromolecules, and regulation of cells by hormones and ions. Work is carried out on both the molecular and cellular level. Techniques include those of biochemistry, physical chemistry, cell biology, and molecular genetics.

- Biochemistry of Gene Expression Section—
  E. Brad Thompson, M.D.

Control of gene expression in eukaryotic cells and its application to clinical medicine are studied. The effects of steroid and other hormones on growth hormone and prolactin induction in cultured cells and cell hybrids are investigated, along with studies on steroid action in human leukemic cells in culture. The molecular details of hormone action are rapidly being learned, providing an excellent model for studying the general question of gene expression in animal cells. In this section, a combination of cell genetic—variant cell lines, hybrids, DNA mediated cell transfections—and biochemical techniques—protein purification, RNA and DNA analysis, DNA cloning—are being used. Clinical applications are made when feasible.

- Biosynthesis Section—
  Edward L. Kuff, M.D., Ph.D.

  Studies on the evolution and functional significance of endogenous retroviral genetic elements, the enzymatic mechanism of DNA synthesis, and the regulation of collagen biosynthesis and secretion in normal and transformed cells are the concern of this section. Technical approaches include analysis of nucleic acid sequence relationships and genomic organization, isolation of subcellular and viral components, purification of DNA polymerases and their use in constructing *in vitro* synthetic systems, and the characterization of enzymes and cofactors involved in sequential processing of newly formed collagen.

- Cellular Regulation Section—
  O. Wesley McBride, M.D.

  Regulation and control of gene expression in eukaryotes is studied using bovine papilloma virus and simian virus 40 as vectors for animal cells. Expression vectors are constructed using recombinant DNA techniques, and control of gene expression is evaluated at the levels of both transcription and translation. In other studies, chromosome- and DNA-mediated gene transfer into heterologous mammalian cells is used to map human genes and to isolate restricted regions of the human genome. Somatic cell hybrids are employed to map various human genes, including immunoglobulin genes, to specific chromosome segments.

- Developmental Biochemistry Section—

  Studies on the biochemical processes in development and differentiation are investigated with particular emphasis on regulatory phenomena. The structure of selected components of the genome of several animal species is studied, as well as gene expression during the development of germ cells and embryos. Currently under study are the functional organization of chromatin in *Drosophila* and genes encoding muscle-specific proteins in chickens.

- Macromolecular Interactions—
  Claude B. Klee, M.D.

  Studies are directed toward the understanding of the mechanism of coupled regulation of cellular processes by Ca^{2+}, calmodulin, and cyclic nucleotides. Enzymes regulated by calmodulin are characterized, and then interaction with calmodulin and other regulatory ligands are studied at the molecular level as well as in eukaryotic cells in tissue culture.

- Nucleic Acid Enzymology Section—
  Maxine Singer, Ph.D.

  Studies pertain to a variety of nucleic acid structural and functional relationships in eukaryotic cells and viruses. Of particular interest is the organization of repetitive sequences in primate DNA, and the relation between the genomes of simian virus 40 and its permissive host.

- Protein Chemistry Section—
  Elbert A. Peterson, Ph.D.

  Studies are in progress on the biochemical changes accompanying differentiation and maturation of leukocytes and the nature of factors controlling these processes; the interactions between cells involved in the immune response and the identification and isolation of participating cell types; and the development of new physical and immunological methods for the purification of cell populations, subcellular organelles, and proteins.

Laboratory of Cell Biology—
L. W. Law, Ph.D

Personnel of this laboratory have diverse interests focusing on the study of transformation of a normal cell to a neoplastic cell. Some of the specific problems pursued are: genetic control of the synthesis of abnormal proteins produced by malignant cells, principally plasma cells; role of cell membranes in regulating differentiation and growth; identification and study of tumor antigens and of the specific immune reactions initiated; solubilization and purification of transplantation and tumor antigens; influence of somatic cell hybridization on expression of genetically determined events; and ultrastructural analysis and molecular biology of viral oncogenesis. Techniques from virology, immunology, immunochemistry, biochemistry, biophysics, tissue culture, somatic-cell hybridization, and electron microscopy are used in these studies.

- Office of the Chief

Investigations are conducted in collaboration with the chemistry unit on the biologic, biochemical, and chemical characteristics of solubilized and purified H-2, HL-A, and tumor antigens on the cell membrane. Studies are also in progress on the immune response of the tumor-bearing animal and response to solubilized tumor antigens.

- Somatic Genetics Unit—
  H.C. Coon, Ph.D.

This unit is studying the genetics and transforming capacity of mitochondrial DNA and the characteristics of somatic cell hybrids, particularly those employing neuron hybrids.

- Chemistry Section—
  E. Appella, M.D.

Biochemical, biophysical, and chemical studies are conducted on solubilizing and purifying tumor antigens and histocompatibility antigens (H-2, HL-A). The unit is also investigating the epoxide hydrase mechanism in the metabolism of chemical carcinogens, the chemistry of Edman degradation, and new supports for solid phase degradation.

- Cell-Mediated Immunity Studies
  Unit—C. C. Ting, M.D.

This unit studies mechanisms of tumor cell killing in syngeneic systems using several cell-mediated assays; also the role of humoral factors, suppressor cells, and helper cells.

- Immunochemistry Section—
  M. Potter, M.D.

This section focuses on the chemistry of immunoglobulins secreted by plasma cell tumors, the factors concerned with initiation and growth of myelomas, and the antibody combining sites of myeloma proteins.

- Ultrastructural Biology Section—
  N. A. Wivel, M.D.

Laboratory investigations focus on factors that contribute to cell differentiation and malignant transformation with particular emphasis on systems where oncogenic viruses represent the carcinogenic agent.

- Viral Oncogenesis Section—
  Kenneth S. S. Chang, M.D., D.Sc.

In vitro and *in vivo* systems are used to study the interaction between oncogenic viruses, principally RNA-contained and host cells with special attention directed to host specificity; the genetic factors influencing susceptibility; the role of endogenous viruses in the etiology of reticulum cell sarcomas; and the characterization of features that distinguish viral structural antigens from tumor-associated antigens in the leukemias.

Laboratory of Immunobiology—
Tibor Borsos, Sc.D.

- Section on Cellular Immunity—
  Berton Zbar, M.D.

Cell-mediated immunologic reactions are studied for their capacity to inhibit the growth and spread of experimental cancers. Mycobacterial adjuvants and murine retroviruses are used to augment host response to tumor cells. A variety of animal and *in vitro* models are being used in attempts to delineate the mechanisms of these reactions.

- Section on Humoral Immunity—
  Tibor Borsos, Sc.D.

Antibody- and complement-mediated cytotoxic reactions are studied for the mechanism of action. The primary goal is to understand the molecular basis of complement action and the molecular basis of cell defense mechanism against complement attack. Purification of antibodies, complement components, cell membrane receptors, and studies of synthetic pathways that control cell membrane integrity are also part of the study.

- Section on Immunopathology—
  Edward J. Leonard, M.D.

Alterations in cellular immune function in pathological conditions are studied. Projects include mechanisms of macrophage activation, serum factors that alter macrophage function, the nature of depressed mononuclear phagocyte chemotaxis in patients and animals with neoplasms, the mechanisms of basophil accumulation in delayed hypersensitivity reactions, and the production and chemical nature of lymphotoxin.

Laboratory of Molecular Biology—
Ira Pastan, M.D.

- Molecular Biology Section—
  Ira Pastan, M.D.

This section studies how hormones, viruses, and toxins enter cells and how this information may be applied in cancer treatment. Studies are under way of the structure and function of genes encoding receptors for hormones and growth factor, and on the mechanism by which transforming proteins control cell behavior, cell growth, and gene expression.

- Biochemical Genetics Section—
  Max Gottesman, M.D.

This section studies (1) the regulation of gene expression in *E. coli* and the bacteriophage lambda, including analyses of the control of transcription initiation, transcription termination, and the stability of proteins in bacteria; (2) DNA recombination in prokaryotes with emphasis on site-specific recombination by the bacteriophage lambda and on transposon excision stimulated by phage P; (3) the construction of new cloning vectors based on the above studies.

- Gene Regulation Section—
  Benoit de Crombrugghe, M.D.

Research on the developmental control of gene expression focuses on the collagen genes, a family of developmentally regulated genes, and includes the identification of regulatory signals in these genes, the genetic and biochemical characterization of their control in various cells, and the construction of vectors to study the expression of cloned DNAs in animal cells.

- Cell Organization Section—
  Seymour Wollman, Ph.D.

Studies are carried out on cellular ultrastructural organization that enables cells to move and carry out receptor-mediated endocytosis, phagocytosis, pinocytosis, and mitosis and on the influence of extracellular matrix on cell structure and function.

- Ultrastructureal Cytochemistry Section—
  Mark Willingham, M.D.

This section focuses on the study of basic cellular mechanisms of cell and organelle movement and function using morphologic techniques, especially electron and light microscopic immunocytochemistry, image intensification microscopy of living cells, and direct microinjection of single cells in tissue culture.

- Membrane Biochemistry Section—
  Kenneth Yamada, M.D., Ph.D.

The structure and function of plasma membrane and extracellular glycoproteins such as fibronectin are examined by biochemical, immunological, and cell biological approaches using normal and malignant cells.

- Developmental Genetics Section—
  Sankar Adhya, Ph.D.

To elucidate the mechanisms of control of gene expression in prokaryotes, genetic and biochemical experiments are conducted to determine how various regulatory molecules function to modulate transcription and/or translation.

- Molecular Cell Genetics Section—
  Michael Gottesman, M.D.

Molecular and somatic cell genetic approaches are used to analyze malignant transformation, growth control, cytoarchitecture, and drug resistance of cultured cells. Techniques employed include mutant isolation, somatic cell hybridization, gene transfer, and molecular cloning.

Laboratory of Pathology—
Lance A. Liotta, M.D., Ph.D.

- Surgical Pathology and Postmortem Section—Ernest E. Lack, M.D.
- Hematopathology Section—
  Elaine S. Jaffe, M.D.
- Cytopathology Section—
  Elizabeth W. Chu, M.D.

- Tumor Invasion and Metastases Section—
  Lance A. Liotta, M.D., Ph.D.
- Biochemical Pathology Section—
  David A. Zopf, M.D.
- Ultrastructural Pathology Section—
  Timothy J. Triche, M.D., Ph.D.
- Viral Oncology and Molecular Pathology Section—
  Peter M. Howley, M.D.
- Image Processing Section—
  Lewis E. Lipkin, M.D.
- Pathological Technology Section—
  Barbara Coolidge

The Laboratory of Pathology of the National Cancer Institute offers a 2- to 3-year training program for residents in pathologic anatomy. This program, which is fully approved for Board certification, provides well-supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology, and neuropathology can be arranged. The research activities of the staff are varied, and participation in clinical or basic research projects is an intrinsic part of the program during elective periods. Research interests of the laboratory include: viral oncology, molecular biology, immunopathology, immunochemistry, mechanisms of metastasis, comparative oncology, and tumor biology.

In addition, the laboratory offers research training in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies of viruses and neoplastic cells.

Laboratory of Pathophysiology—
Pietro M. Gullino, M.D.

A group of projects concerning the mammary gland is carried on in connection with the Office of the Chief. Richard Knazek, M.D., Ph.D. studies the mechanism of prolactin action and role of prostaglandins on hormone receptor development. Barbara Vonderhaar, Ph.D. evaluates the role of thyroid hormon-prolactin interactions on mammary gland development and tumorigenesis. Pradman Qasba, Ph.D., using recombinant DNA technology, is studying the expression of differentiated functions during growth and regression of normal and neoplastic mammary glands, and P.M. Gullino, M.D. works on the mechanism and prognostic value of angiogenesis in neoplastic and preneoplastic tissues.

- Section on Cellular and Molecular Physiology—Herbert L. Cooper, M.D.

This section studies the biochemical mechanisms that control early stages of cell growth induction in normal and neoplastic human cells. Emphasis is on the mechanisms which maintain physiologically resting cells in the nongrowing condition and the early biochemical modifications that occur on growth stimulation. Current studies examine translational controls and post-translational protein modifications in human lymphocytes and the specific protein synthetic responses to growth regulatory agents, such as interferon.

- Section on Cell Cycle Regulation—
  William Kidwell, Ph.D.

Laboratory investigations are concerned with characterization of biologic events uniquely required for the cell to progress through S, G_2, M, G, and G_0 phases. Emphasis is placed on the nutritional, hormonal and other factors involved in initiation of cellular transition through division to a differentiated state and the interrelationship among various organ cell types in this progressive change. Specific studies relate to the interaction of epithelial, myoepithelial, and stromal cells, and adipocytes in the proliferative response of the mammary gland to hormones.

- Section on Cellular Biochemistry—
  Yoon Sang Cho-Chung, M.D., Ph.D.

This section studies the mechanisms controlling cell growth and regression. Emphasis is placed on the roles of cyclic nucleotides, hormones, and other intracellular mediators in the growth control of normal and neoplastic cells. Current studies involve the mechanism of action of cyclic nucleotides in the regression of mammary tumors and suppression of mammary carcinogenesis.

- Section on Membrane Biology—
  Pedro Pinto da Silva, Ph.D.

This section investigates the structure and dynamics of biological membranes, using freeze-fracture and freeze-etch electron microscopy alone or in combination with cytochemical labeling techniques.

- Section on Radiation Biology—
  Peter Riesz, Ph.D.

The section is involved in the use of radiation to destroy bone marrow in order to study the laws governing marrow transplantation from donors. The effects of ionizing and UV radiation on nucleic acids and proteins are also being studied. The role of free radicals in biology is being investigated by electron spin resonance and spin-trapping.

Laboratory of Mathematical Biology—
Charles DeLisi, Ph.D.

- Membrane Structure and Function—
  Robert P. Blumenthal, Ph.D.

This section investigates the dynamics of membrane components (lipids, proteins) in biological membranes and in reconstituted lipid-protein systems using a variety of biophysical techniques. Current studies examine how proteins are inserted into membranes, how membranes fuse, and how given membrane components are maintained in specific domains such as apical and basolateral surfaces in epithelial cells.

- Theoretical Immunology—
  Charles DeLisi, Ph.D.

Research areas include the following: (1) theories of receptor function and physical chemistry, with emphasis on the analysis of data bearing on exocytosis, endocytosis, and chemotaxis; (2) analysis of immunoassays and related techniques; (3) cancer epidemiology; and (4) development of mathematical tools necessary to understand collective interactions in complex systems, especially regulation of immune response dynamics.

- Molecular Structure, Properties, and Function—Robert L. Jernigan, Ph.D.

Biopolymers and their conformations and properties are investigated from a theoretical viewpoint. Studies of proteins include enumerations of favorable pathways for achieving native protein conformations. The basic research consists primarily of developing new methods to treat such problems of current interest in molecular biology. Applications, which are typically computer intensive, include globular proteins, membrane proteins, structural proteins, and DNA translation products. DNA flexibility and its origin and effect on physical properties is another area of interest.

- Immunopharmacology—
  John N. Weinstein, M.D., Ph.D.

Monoclonal antibodies (and their conjugates with toxins, radionuclides, and liposomes) are investigated for diagnosis and treatment of cancer. The approach is eclectic, involving membrane biophysics and biochemistry, immunochemistry, *in vitro* cell studies, *in vivo* animal pharmacology, and theoretical modeling. Current emphasis is on delivery to lymphoma and metastases in lymph nodes.

Laboratory of Genetics—
Michael Potter, M.D.

Much of hte focus of research is on the role of genes that determine susceptibility and resistance to neoplastic development and special genes and their products that are associated with the neoplastic state (oncogenes, retroviral gene products, tumor associated antigens). The laboratory has had a long association with the study of the plasma cell tumor system in mice. Research continues on the organization of immunoglobulin genes, and gene families and structure function correlations with monoclonal antibodies.

Current ongoing projects concern: expression of the myc (and other) oncogenes in lymphomas and plasmacytomas; immunoglobulin V_K and V_H gene families in the genus *Mus*; structure and identification of contact amino acids in phosphorylcholine; lysozyme and galactan binding monoclonal antibodies; pathogenesis of erythroleukemia in mice; thyroglobulin producing cell lines; isolation and characterization of unique tumor associated antigens; and the search for genes that control susceptibility to plasmacytomagenesis in BALB/c mice.

The laboratory can provide research training in amino acid and DNA sequences, recombinant DNA technology, tissue culture, hybridoma-monoclonal and antibody production.

Laboratory of Tumor Immunology and Biology—
Jeffrey Schlom, Ph.D.

The laboratory conducts research to identify immunologic markers specific for, or associated with, various human neoplasms, with the ultimate aim of applying these toward the diagnosis, prognosis, and treatment of human cancer. Specifically, the laboratory is engaged in studies involving the generation and characterization of monoclonal antibodies to tumor associated determinants with particular emphasis on the study of human carcinomas. Studies ongoing involve the conjugation of monoclonal antibodies to isotopes or toxins, to aid in the diagnosis, localization, and potentially the elimination of tumor cells. Immunoassays are being developed that will aid in the characterization of human tumor cell populations, and in the diagnosis or prognosis of certain human cancers. The laboratory is also engaged in studies to investigate the association between specific murine and human genetic elements and tumorigenesis, employing techniques of gene cloning and molecular hybridization.

- Experimental Oncology Section—
  Jeffrey Schlom, Ph.D.

Projects under way include research to generate and characterize monoclonal antibodies that are reactive with mammalian carcinoma cells with emphasis on human breast and colon carcinomas; to use monoclonal antibodies to identify and characterize specific proteins that are associated with the neoplastic state, with emphasis on human carcinoma systems; and to develop immunoassays that will aid in the characterization of human carcinoma cell populations and in the diagnosis or prognosis of human carcinomas. The use of monoclonal antibody, conjugated with isotopes, is being investigated to aid in the detection or therapy of carcinoma lesions. Experiments are being conducted to determine those factors which influence the antigenic modulation, antigenic phenotype, and the state of differentiation of human carcinoma cell populations.

- Oncogenetics Section—
  Robert Callahan, Ph.D.

This section seeks to identify and molecularly clone tumor specific cellular and viral genetic elements from human carcinoma and other mammalian tumors. Research is being conducted to determine the organization of tumor specific genetic elements in cellular DNA, and the biological activity and role of tumor specific genes in normal and neoplastic tissue. The ultimate aim is to develop an understanding of the genetic changes which are relevant to the etiology of human neoplasia.

- Biochemistry of Oncogenes Section—
  Robert Bassin, Ph.D.

Investigations of the mechanisms of cellular transformation mediated by RNA tumor viruses and by related cellular oncogenes are under way, emphasizing the nature and functions of specific cellular proteins which are involved in the transformation process. Studies are being conducted to identify genetic elements responsible for tumorigenesis and for immunologic markers specific for various human carcinomas. Studies are also being carried out to investigate the cellular control mechanisms which are active in preventing infection and disease by endogenous RNA tumor viruses.

Division of Cancer Cause and Prevention, NCI

Richard H. Adamson, Ph.D., Director

The Division of Cancer Cause and Prevention plans and directs a national program of laboratory, field, and demographic research on the cause and natural history of cancer and means for preventing cancer through direct intramural research, research grants, and contracts;

evaluates mechanisms of cancer induction and promotion by chemicals, viruses, and environmental agents; serves as the focal point for the Federal Government on the synthesis of clinical, epidemiologic, and experimental data relating to cancer; and participates in the evaluation of and advises the institute director on program-related aspects of the other grant and cancer control activities as they relate to cancer cause and prevention.

Carcinogenesis Intramural Program—
Richard H. Adamson, Ph.D.
Acting Associate Director

The Carcinogenesis Intramural Program conducts a basic laboratory research program on the causes of cancer by chemical, physical, and biological (viral) factors; and on the pathogenesis and prevention of various cancers.

Laboratory of Carcinogen Metabolism
Snorri S. Thorgeirsson, M.D.,

The Laboratory of Carcinogen Metabolism conducts investigations on (1) the metabolic processing of various classes of chemical carcinogens, such as aromatic amines and amides; (2) the relationship between chemically induced mutations and carcinogenesis; (3) control of gene expression during chemically induced tumor formation; and (4) the role of modifiers of differentiation in the inhibition or promotion of tumor formation.

Laboratory of Cellular and Molecular Biology—
Stuart A. Aaronson, M.D.

The program of the Laboratory of Cellular and Molecular Biology is primarily focused on defining the factors contributing to oncogenesis at the molecular level. Major emphases are on the molecular mechanisms involved in RNA tumor virus-induced cancers and isolation and characterization of human oncogenes. Techniques employed include gel electrophoresis, restriction enzyme analysis, Southern blotting technique, electron microscopy, immunology, genetics, and tissue culture. Materials utilized in studies include animal retroviruses including transforming sarcoma viruses, normal fibroblasts and epithelium from genetically compromised individuals at high risk for cancer and cells derived from human and animal cancers. Disciplines represented within the laboratory include virology, immunology, biochemistry, cell biology, and molecular genetics. Ongoing collaborations include, in addition to the above, oncology and epidemiology.

Laboratory of Human Carcinogenesis—
Curtis C. Harris, M.D.

The Laboratory of Human Carcinogenesis conducts investigations to assess (a) mechanisms of carcinogenesis in epithelial cells from humans and experimental animals, (b) experimental approaches in biological systems for the extrapolation of carcinogenesis data and mechanisms from experimental animals to the human situation, and (c) host factors that determine differences in carcinogenic susceptibility among individuals.

Medical staff fellows spend 2 to 3 years in the laboratory investigating problems in three areas (examples of studies are also listed):

Molecular and Biochemical Epidemiology—Measurement of gene polymorphism by molecular approaches to identify host susceptibility factors that predispose to cancer; measurement of carcinogen-DNA adducts and other carcinogen-induced lesions in biological samples from individuals in environments associated with high and low risk for cancer; and studies of interactions between the effects of cocarcinogens and carcinogens.

Carcinogen Macromolecular Interaction—Identification of metabolic pathways kof carcinogen activation and deactivation; inter- and intragenic damage and rearrangements caused by chemical and physical carcinogens; and determination of the importance of repair of carcinogen-induced damage to DNA and chromosomes in carcinogenesis.

In Vitro Carcinogenesis—Investigation of the mechanisms of neoplastic transformation; studies of phenotypic and genetic alterations during *in vitro* carcinogenesis; assessment of the relationship between carcinogenesis, mutagenesis, and differentiation in mammalian cells; and identification of extra-, inter- and intracellular factors modulating growth and differentiation of human epithelial cells.

Medical staff fellows may also participate in combined laboratory-epidemiology studies and are encouraged to collaborate with epidemologists.

Laboratory of Molecular Virology—
George Khoury, M.D.

The Laboratory of Molecular Virology is primarily interested in the normal and abnormal regulation of gene expression. A number of systems are employed in an attempt to determine in specific cases what signals regulate gene expression. At present, the laboratory is particularly interested in both viral and eukaryotic genetic units. In particular, the research efforst are focusing on genes which are regulated at the level of transcription which in some cases are responsive to induction by hormones or other stimuli. In addition, the laboratory has made a commitment to the study of oncogenes and the mutations which are responsible for the activation of these genes in neoplasia. Studies are being pursued on the histocompatibility antigens in hopes of determining the role of these genes in immune surveillance and tumor immunity.

Laboratory of Viral Carcinogenesis—
George J. Todaro, M.D.

The Laboratory of Viral Carcinogenesis plans and implements basic laboratory research programs aimed at delineating the mechanisms of malignant transformation. Studies are conducted on the origin, chromosomal location, characteristics, and interactions of viral and cellular genes for oncogenicity, differentiation and susceptibility leading to the specific genes' isolation, characterization, and replication through recombinant DNA technology. Investigations are under way on these molecular and genetic processes using viruses as the models and tools for understanding the evolution and control of cancer. The laboratory is also studying the nature of hormone-like tumor-growth factors, tumor-inhibitory factors, and tumor promoters to determine their relationship to malignant genes and to the progressive stages of transformation of cells *in vitro* and *in vivo*. Since some classes of these factors clearly accelerate transformation or inhibit or reverse the process, they present attractive opportunities to explore further research and clinical applications.

Field Studies and Statistics Program—
Joseph F. Fraumeni, Jr., M.D.
Associate Director

Medical staff fellow positions are available for 2-year assignments in the three branches of the Field Studies and Statistics Program, which provides the focus for epidemiologic and biostatistical research within the Institute. The program conducts epidemiologic investigation into the environmental and host determinants of human cancer; coordinates a network of population-based cancer registries for evaluating cancer incidence, mortality, and survival in the United States; analyzes the natural history of cancer and the efficacy of therapeutic and preventive measures; and designs statistical models for clinical and experimental investigations.

Environmental Epidemiology Branch—
Robert N. Hoover, M.D., Acting

The Environmental Epidemiology Branch conducts studies to clarify the risk of cancer among persons exposed to occupational, nutritional, medicinal, radiogenic, infectious or other environmental hazards, and among persons with genetic or immunologic predisposition.

Clinical Epidemiology Branch—
Robert W. Miller, M.D.

The Clinical Epidemiology Branch investigates the origins of human cancer by starting from peculiarities of cancer occurence recognized at the bedside and studied through the disciplines of clinical medicine, epidemiology, and cellular genetics and other laboratory sciences. Current emphasis is given to the clinical delineation of cancer family syndromes and disorders that predispose to cancer, such as neurofibromatosis and certain birth defects, and to studies evaluating the late effects of cancer treatments, including reproductive toxicity. Liaison is maintained with many clinical services throughout the Washington area and beyond, as well as with the NIH Interinstitute Medical Genetics Program. Physicians selected for this program may become Board-eligible in medical genetics, but need not have specific training in genetics or epidemiology.

Division of Cancer Treatment
Bruce A. Chabner, M.D., Director

This Division carries out a broad program of basic and clinical research concerning the treatment of cancer. The major areas of research are radiation therapy, drug therapy, modifiers of tumor growth and differentiation, and surgical approaches to cancer treatment. Treatment programs are multidisciplinary in nature, involving the cooperative efforts of medical, surgical, and radiotherapy staff members.

Cancer Therapy Evaluation Program—
Daniel Hoth, M.D., Acting Associate Director

One medical staff fellow position is open each year within the Cancer Therapy Evaluation Program. The fellow is assigned to the Investigational Drug Branch for 1 year. Subsequently, a second year program may be developed in conjunction with other branches or laboratories within the Division of Cancer Treatment, or within the Cancer Therapy Evaluation Program by rotating to the Clinical Investigations Branch. It is anticipated that the second-year medical staff fellow will also maintain some responsibility for drug monitoring. Eligibility for a third year within the program is feasible. The duties within the Investigational Drug Branch include developing and coordinating clinical research efforts on specific new antineoplastic drugs developed by the NCI. Special projects in the area of antineoplastic drugs are available. The work within the Clinical Investigations Branch includes monitoring research and progress in grant and cooperative agreement programs, reviewing new research protocols, developing new research strategies along disease or modality lines, providing overviews of research topics, and planning discussion groups and intergroup studies.

The major function of the Cancer Therapy Evaluation Program is to sponsor clinical trials of investigational and known antineoplastic treatment modalities and to monitor those trials with investigational chemotherapeutic agents to a disease-oriented approach. This includes the incorporation of effective chemotherapeutic combinations in early stages of disease and testing of new modalities, such as immunotherapy in combination with surgery, radiotherapy, and chemotherapy in specific disease entities until now considered untreatable. For these purposes, the program has planned and helped organize several study groups designed to test combined modality approaches to specific diseases. The program also supports, through the cooperative agreement mechanism, various clinical cooperative groups made up of institutions of higher education. These cooperative groups share in the design, development, execution, and analysis of clinical protocols. The program encourages and sponsors disease-oriented meetings with representatives from all interested groups to achieve coordination of clinical research efforts at a national level. Staff members of the program periodically attend meetings of the clinical cooperative groups, disease-oriented task forces, and working parties. In addition, the program serves as a vehicle of communication between in-house preclinical and clinical programs and extramural activities.

The program coordinates clinical conferences sponsored by the chemotherapy area, which is an important mechanism for informing clinical investigators throughout the world on the status of drug trials. The conferences are held to discuss the clinical programs concerned with drug development. The program also maintains a special relationship with the Clinical Oncology Program's branches, the Biological Response Modifiers Program, and the Radiation Research Program. In addition, it is responsible for the development of new areas of clinical research and dissemination of information on clinical trials to investigators in foreign countries, and is responsible for receiving and analyzing information from abroad.

Clinical Investigations Branch—
Edwin Jacobs, M.D., Acting

The Clinical Investigations Branch monitors and coordinates a broad range of research activities. This includes research support for individual investigator-initiated projects (R01), program project grants (P01), cooperative group agreements (M10), and planning grants (P20). This research spans the spectrum from laboratory research to phase III clinical trials. Staff responsibilities include critical review and participation in the development of protocols developed by cooperative groups of protocols for contract groups and intergroup studies. Staff members also develop overviews of research progress, formulate strategies for future research directions, and plan discussion groups on selected topics. There is a major emphasis on integration of modalities in the treatment of cancer.

This branch also maintains liaison with international clinical research groups and the Breast Cancer Task Force.

- Medicine Section—
  John Y. Killen, Jr., M.D.

This section reviews, monitors, and coordinates studies related to medical oncology and hematology, including studies of supportive care, basic investigations, and clinical trials. Members evaluate and stimulate research in chemotherapy (Phase II and III) and in the design of comprehensive therapeutic programs aimed at improving response to therapy and increasing the cure rate for specific neoplastic diseases.

- Nutrition Section—
  Edwin Jacobs, M.D., Acting

This section plans, develops, evaluates, and administers grant- and cooperative agreement-supported research concerning the role of nutrition in the care and treatment of cancer patients. Areas of interest include the mechanisms of nutritional derangement in cancer patients, the prognostic effect of altered nutritional status, the application of basic nutritional research to the cancer patient, and the development of innovative approaches to the nutritional management of cancer patients.

- Pediatric Section—
  Richard Ungerleider, M.D.

This section is responsible for review, evaluation, and stimulation of multimodal approaches to the treatment of childhood malignancies. This includes development and monitoring of phase I-II clinical trials in pediatric malignancies, liaison with investigators at cancer centers treating childhood malignancy, and monitoring and interacting with investigators in the Clinical Cooperative Groups involved in pediatric cancer.

- Surgery Section—
  Ernest DeMoss, M.D.

This section plans, evaluates, and administers grant-supported research concerning the role of surgery in the care and treatment of cancer patients. Topic areas of interest include evaluation of new or modified surgical techniques; development of techniques for vascular infusion, perfusion, and occlusion; tumor immunology; biology of metastases; staging procedures; and evaluation of prognostic factors in the surgical treatment of cancer patients.

Investigational Drug Branch—
Silvia Marsoni, M.D., Acting

This branch monitors and coordinates the drug-oriented trials of the Division. The branch serves as a link between the preclinical and clinical aspects of the drug development part of the Division with special interest in the pharmacologic investigations of new drugs. Interaction with investigators is a vital part of the work of the branch in providing supervision, advice, and retrieving information on therapeutic response and toxicity.

- Regulatory Affairs Section—
  Daniel Hoth, M.D., Acting

The section provides liaison with the Food and Drug Administration and supervises the preparation of all FDA filings on new drugs. This involves a close working relationship with intramural branches and committees dealing with submission of data to meet regulatory requirements.

- Drug Evaluation and Reporting
  Section—Silvia Marsoni, M.D.

The section reviews, coordinates, and monitors protocol studies for phase I and early phase II clinical trials supported under contract. The section prepares annual reports on IND drug studies and investigates and reports on Adverse Drug Reactions.

- Drug Management and Authorization
  Section—Clarence Fortner, M.S.

This section authorizes the distribution of NCI-sponsored investigational new drug agents to eligible investigators and administers the program of accountability for the use of investigational drugs distributed under NCI sponsorship. It assures that the FDA regulatory requirements for the distribution of investigational agents are met.

- Biologics Evaluation Section—
  Luz Hammershaimb, M.D., Acting

This section develops plans for Phase II and III trials with biological response modifiers and interacts with investigators and the pharmaceutical industry in designing these trials. It monitors the clinical trials of biological agents sponsored by NCI and provides annual reports to the FDA.

- Quality Assurance Compliance
  Section—Danial Hoth, M.D., Acting

The responsibility of this section includes managing the site visit monitoring program for all clinical trials using NCI-sponsored agents, coordinates all monitoring activities within the clinical cooperative groups, and provides information to all NCI clinical investigators regarding FDA regulations, NCI policies, procedures, and human subjects regulations.

Radiotherapy Development Branch—
David A. Pistenmaa, M.D., Acting

The Radiation Research Program (RRP) was established in May 1982 and consists of the Diagnostic Imaging Research Branch, the Low-Level Radiation Effects Branch, and the Radiotherapy Development Branch. The program is responsible for the support of extramural preclinical and clinical research in imaging therapy with ionizing and nonionizing radiations as well as the biological and health effects of ionizing and nonionizing radiations. The RRP has no intramural research component. Thus, someone who chooses to spend time in the RRP would be involved primarily with the planning, management, and evaluation of those aspects of the $60 million grant- and contract-supported research program in which he or she has interest. This experience might be especially valuable for someone interested in academic medicine who would be expected to seek grant or contract support for research in later years.

Clinical Oncology Program—
Samuel Broder, M.D.
Associate Director

The Clinical Oncology Program (COP) recruits approximately 18 medical staff fellows each year for a 3-year assignment in medical oncology or a 2-year assignment in surgical oncology. Fellows are recruited for one of the following clinical branches: Medicine, Pediatric Oncology, Radiation Oncology, and Surgery, located in the NIH Clinical Center on the Bethesda campus, or NCI-Navy Medical Oncology Branch located at the National Naval Medical Center, Bethesda, Maryland. The program also offers a residency training program in radiotherapy.

The 3-year medical oncology training program is offered to candidates who have at least 2 years of postgraduate training (internship and first-year residency) in medicine or pediatrics. The first year consists of primary responsibility for the clinical care of both inpatients and outpatients. The staff fellow may sometimes take a full year with a single clinical service, or take two 6-month rotations through the clinical services of the COP. The second and third years consist of clinical and/or laboratory research under the supervision of a member of the senior staff. Medical staff fellows will have the opportunity to select a project from the numerous current studies in the laboratories of the Clinical Oncology Program, the Developmental Therapeutics Program, or the Biological Response Modifiers Program. Opportunities are also available for clinical trial monitoring in the Cancer Therapy Evaluation Program. Clinical electives are available on consultative services in the branches and other related departments, and in various procedures, such as peritoneoscopy. Second- and third-year medical staff fellows continue to follow patients in the Outpatient Department. Offered throughout the program are lectures, clinical conferences, research seminars, teaching rounds, and joint conferences relevant to the field of clinical oncology and cancer research. Certain clinical conferences are mandatory.

Candidates otherwise qualified who successfully complete the program are eligible for Board certification in the subspecialty of medical oncology or pediatric hematology-oncology.

For further information, applicants to the medical or pediatric oncology training programs should write to:
Associate Director
Clinical Oncology Program
National Cancer Institute,
Building 10, Room 6B15
Bethesda, MD 20205.

The Surgery Branch offers a 2-year surgical oncology training program. This program consists of a 6-month period on the wards of the Surgery Branch, inpatient and outpatient services, and 1½ years in one of the laboratories of the senior staff in the Surgery Branch. Selected medical staff fellows may remain for a third year to continue their laboratory research. Applicants interested in the Surgery Branch program should write director Steven Rosenberg, M.D., Ph.D., Surgery Branch, Building 10, Room 10N116, National Cancer Institute, Bethesda, MD 20205.

Applicants interested in the radiotherapy residency should write to Eli Glatstein, M.D., Radiation Oncology Branch, Building 10, Room B3B69, National Cancer Institute, Bethesda, MD 20205.

Clinical Pharmacology Branch—
Charles Myers, M.D.

This group conducts laboratory and clinical research activities on problems of drug action and toxicity in man and, as such, plays a supporting role for the chemotherapy programs of the other clinical branches of the NCI. The branch does not have patient care responsibilities of its own, but accomplishes its clinical studies through collaborative ties with the other clinical branches. Research training opportunities are available for physicians completing 1 year of clinical training in the Clinical Oncology Program or for trainees of the Clinical Pharmacology Training Program of the National Institute of General Medical Sciences.

Areas of specific research interest include: mechanisms of adriamycin cytotoxicity; mechanism of action and cellular pharmacology of antimetabolites; pharmacokinetics and metabolism of established and new antineoplastic agents; clinical and experimental applications of cytofluorometry; and molecular genetics of drug resistance.

Medicine Branch—
Robert C. Young, M.D.

The Medicine Branch is an adult medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of the malignant lymphomas, Hodgkin's disease, breast cancer, ovarian carcinoma, sarcomas, melanoma, endometrial cancer, chronic leukemias, and testicular cancer. Training in clinical diagnostic procedures such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH, such as cancer surgery and radiation therapy. The Branch has an active autologous marrow infusion program.

The branch conducts weekly clinical conferences with the departments of radiation oncology, pathology, clinical pathology (hematology), and radiology on current problems and on the staging of lymphomas, Hodgkin's disease, and testicular carcinoma. Research focuses on the general areas of kinetics and cytogenetics of neoplastic and hemopoietic cells, immunological alterations induced by disease or chemotherapy, and the biochemical pharmacology of antineoplastic agents. In addition, an active research program is under way in the field of hormone receptors, tumor markers, and tissue culture. The branch conducts weekly laboratory conferences, in conjunction with the Clinical Pharmacology Branch, on laboratory topics of mutual interest. Collaboration with the Clinical Pharmacology Branch and other laboratory groups is maintained.

NCI-Navy Medical Oncology Branch—
John D. Minna, M.D.

The NCI-Navy Medical Oncology Branch is located at the National Naval Medical Center (NNMC) in Bethesda, Maryland across the street from the NIH Clinical Center. This branch is part of the NCI intramural Clinical Oncology Program and, with the Navy Hematology-Oncology Branch (Steven Veach, M.D., Chief), part of the NNMC cancer treatment program. The NNMC is a 450 bed tertiary referral hospital for active duty military, military retired, and military dependents. Patients are referred from around the world with all types of malignant diseases including solid tumors (e.g. lung, breast, gastrointestinal) and hematologic malignancies (Hodgkin's disease, non-Hodgkin's lymphomas, and acute and chronic leukemias). There is a large population of young adults with such malignant diseases as germ cell tumors. The program has a 20-bed inpatient service, and also provides consultation in oncology and hematology to the NNMC (approximately 40-60 active inpatients at any one time). In addition, civilian patients who are eligible for certain NCI studies can be admitted to the program for care and study. The NCI-Navy Medical Oncology and Navy Hematology-Oncology Branches represent a joint and integrated NCI-Navy effort in cancer patient care, clinical and laboratory investigation, and training in clinical oncology and hematology. More than 1,000 patients are followed by the NCI-Navy Program in a study and primary care setting and each fellow has approximately 100 patients as his or her primary care responsibility. Most fellows spend 6 months at the Clinical Center, NIH, and 6 months at the NNMC during the clinical year. The clinical research studies involve a wide variety of diseases and represent a collaboration between the intramural Clinical Oncology Program Branches and the NNMC.

The laboratory investigations of the branch revolve about human tumor cell biology and include studies of cell culture, somatic cell hybridization, cell kinetics, molecular biology, production of monoclonal antibodies by hybridomas, identification of tumor cell growth factors and pathways of differentiation, and human tumor cell genetics using gene transfer techniques. A major effort involves growing tumors from individual patients and selecting therapy after *in vitro* drug and radiation therapy sensitivity testing (human tumor clonogenic assay). The program is designed to include clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interest and goals.

Pediatric Oncology Branch—
Philip A. Pizzo, M.D.

The Pediatric Oncology Branch conducts clinical and laboratory research activities related to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, Ewing's sarcoma and neuroblastoma. Children and adolescents are accepted for treatment. Three areas of clinical investigations are stressed: chemotherapy with new or established agents; hematologic support and bone marrow transplantation; and diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 30 inpatient beds and an extensive outpatient department. The branch also has an extremely active teaching program, with 12 weekly clinical and laboratory conferences and seminars. Candidates with prior training in pediatrics may apply to this branch and are eligible for Board certification in pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical, surgical, and/or radiotherapeutic means, followed by experimental manipulation to prolong remission.

Comprehensive immunologic assays are performed to assess the natural history of these diseases and the influence of treatment.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. In conjunction with the Medicine Branch, a major area of interest is hematologic reconstitution through autologous bone marrow and stem cell transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised patient. These maneuvers include the use of laminar-air-flow isolation and prophylactic antimicrobial agents, as well as methods to bolster host defenses.

In the second and third year of this program, clinical research training is offered in the areas previously described. In addition to clinical research, the branch has a strong program in basic laboratory investigation with emphasis on tumor cell biology, molecular biology, clinical pharmacology, tumor immunology, hematopoiesis, and immunoregulation.

Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates by utilizing excellent collaborative relations with other branches of the NIH.

Radiation Oncology Branch—
Eli Glatstein, M.D.

The Radiation Oncology Branch of the National Cancer Institute offers a 3-year training program in radiation oncology. This program is organized in conjunction with the Uniformed Services University of the Health Sciences, through Walter Reed Army Medical Center and the National Naval Medical Center in Bethesda. The program calls for 18 months at the NCI, 9 months at Walter Reed, and 9 months at the NNMC.

The program emphasizes all aspects of patient care in radiation therapy with major emphasis on treatment planning and dosimetry. Experimental approaches are emphasized within the National Cancer Institute as part of prospective clinical trials; conventional treatment approaches are emphasized at the military facilities. Work on radiation sensitizing compounds, radioprotecting compounds, intraoperative irradiation, and atypical fractionation schemes will be ongoing at NCI. Areas of investigation include primary breast cancer, pancreatic carcinoma, carcinoma of the bladder, small call carcinoma of the lung, lymphoma, Hodgkin's disease, gliomas, mycosis fungoides, soft tissue sarcomas, and pediatric neoplasms. Opportunities for study of a wider spectrum of conditions are available through the military hospitals, with special attention to head and neck cancer and gynecologic neoplasms. The emphasis at all institutions will be on combined modality approaches and on long-term follow-up to assess success and morbidity.

Preference will be shown to candidates who have completed all or part of training in another oncologic specialty. The director of training for the program is Eli Glatstein, M.D., Radiation Oncology Branch, National Cancer Institute. Interested individuals should contact him.

Surgery Branch—
Steven A. Rosenberg, M.D., Ph.D.

This branch, a surgical oncology unit, emphasizes a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen, including sarcomas, rectal, breast, esophageal, and pancreatic cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy, as well as the development of new surgical techniques. Laboratory efforts are closely related to clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, X-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch physicians also serve as general surgeons to the entire NIH and see a variety of general surgical consultations not related to the field of cancer.

Developmental Therapeutics Program—
John Driscoll, Ph.D., Acting Associate Director

This program is a broadly based endeavor which promotes and supports all pertinent activities essential to preclinical development of new treatment modalities for cancer, particularly chemotherapy. A systematic search is conducted for potential antitumor agents. These are subjected to programmed preclinical evaluation according to a scheme called the Linear Array. In this approach the program is responsible for all preclinical phases of development including acquisition and synthesis of materials, isolation and production of diverse natural products, screening, pharmaceutical development, toxicology, and pharmacology.

The Office of the Associate Director is responsible for overall administration of a large intramural research program and an extramural program on preclinical development of therapeutic modalities.

Medical Staff Fellows

First-year medical staff fellows in the Clinical Oncology Program are eligible to work in the laboratories of the Developmental Therapeutics Program (DTP) for their second and third years of research training. The following paragraphs describe current projects from which medical staff fellows may elect to participate.

Laboratory of Chemical Pharmacology—
Richard L. Cysyk, Ph.D., Acting

This laboratory brings together scientists who play an important role in the use of pharmacologic information—plasma levels, tissue levels, mechanism of action, transport and metabolism studies—for experimental chemotherapy and earlier development and use of cancer chemotherapeutic agents for the clinic.

The pharmacologic properties of potential and established antitumor agents are evaluated *in vitro*, in animals and humans. These studies include evaluation of the antitumor activity of single agents, adjuvant and combination chemotherapy, and other modalities for cancer therapy. Other studies involve investigations on mechanism of action, structure-activity relationships, transport, dose-response relationships, effects on the immune system, mutagenic and carcinogenic potential of antitumor agents, and their disposition in laboratory animals and humans. The latter studies include the establishment of rates and rate constants that govern the passage of drugs from one body compartment to another.

Laboratory of Medicinal Chemistry and Biology—
David G. Johns, M.D., Ph.D.

This laboratory conducts an integrated program on the development of antitumor agents. Compounds with potential antitumor activity are synthesized, and effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites, e.g., nucleic acids, nuclear proteins, microtubular protein, and enzyme systems. Analytical methodology for *in vivo* studies with new agents is developed and, where warranted, biological studies with these agents are extended to the preclinical and phase I stages. A contract-supported program to characterize the mode of action of new antitumor agents is also managed here. This laboratory stresses rapid and continuous utilization of the data generated from biological studies for elucidation of structure-activity correlations for guidance in synthesis of new antitumor agents of potential clinical value.

Laboratory of Molecular Pharmacology—
Kurt W. Kohn, M.D., Ph.D.

Mechanisms of action of anticancer agents are studied in culture and subcellular systems with particular attention to effects involving DNA and nuclear proteins. These investigations focus on the relation between drug-induced macromolecular damage (and its repair) and cell survival. Secondly, drugs are used as probes of the structure and function of DNA and chromatin. Experimental approaches include cell culture, DNA macromolecular damage measurements, and nuclear protein fractionation techniques.

Laboratory of Experimental Therapeutics and Metabolism—
Michael R. Boyd, M.D., Ph.D.

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is in analytical and clinical pharmacology; qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents are studied in experimental systems, as well as in man in a clinical setting. Problems are selected for their relevance to the development and/or evaluation of new chemotherapy protocols, and frequently are pursued collaboratively with other NCI laboratories. The other major area concerns the elucidation of fundamental chemicobiologic interactions underlying chemical-induced cytotoxicity and carcinogenicity to specific target organs and target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target tissue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic "activation" and "deactivation" systems are of interest as well as investigation of the biochemical, physiologic, and morphologic consequences in the *in situ* generation of alkylating metabolites both in normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemical-induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimal toxicity to normal tissues.

Laboratory of Tumor Cell Biology—
Robert C. Gallo, M.D.

The objectives of the Laboratory of Tumor Cell Biology are to develop, implement, and analyze data obtained from studies of cell proliferation, cell differentiation, and biochemical growth characteristics of normal and malignant mammalian cells both *in vivo* and *in vitro*. Particular attention is given to hematopoietic cells, their normal behavior, and especially changes seen during leukemogenesis. Because of unusual access to human blood cells and because of the interest of this group, there is special focus on human leukemias and lymphomas. It is anticipated that an enhanced understanding of cell regulatory mechanisms will permit the optimal use of antitumor agents in the therapy of cancer and the development of new approaches.

The Laboratory of Tumor Cell Biology is concerned with several biological and biochemical problems: (1) Studies on the cellular and molecular origin and pathogenesis of human leukemia. Biochemical control mechanisms involved in cell differentiation and neoplastic transformation are examined. Tumor viruses of animals are used both as tools (to define and isolate genes and gene products important for growth in man) and to understand mechanisms of naturally occurring animal leukemias. Also, studies designed to determine if humans have similar viruses (retroviruses) are and have been intensively studied. (2) Studies on the biochemical events preceding mitosis. An understanding of these events appears essential to the control of proliferation, and information derived from such studies may lead to more effective inhibitors of neoplastic cell growth. Events leading to mitosis are also of interest since many of the effective antitumor agents are useful only when cells are in DNA replication or in mitosis. Phytohemagglutinin-stimulated human lymphocytes and tissue-cultured cells are the principal tools in these studies. (3) Attempts to develop new approaches to cancer chemotherapy using information gained from basic cellular studies. (4) Studies on the development of biochemical and immunologic markers for malignant cells are carried out. Biochemical and immunologic studies are also conducted in individuals with disorders associated with an increased incidence of neoplasia. (5) Controls regulating cell growth and differentiation, and the process of malignant transformation in hematopoietic cells. (6) Growth factors (and their receptors) that control the growth and differentiation of blood cells have been isolated and are under intensive study, e.g., T-cell growth factor (TCGF), CSF, and related hematopoietic growth affecting molecules.

NCI Informational Bulletin

Prospective applicants to the National Cancer Institute may obtain an NCI Informational Bulletin by writing Alan Rabson, M.D., Director, DCBD, NCI, Building 31, Room 3A03, National Institutes of Health, Bethesda, MD 20205.

National Eye Institute

Carl Kupfer, M.D.,
Director
Elmer J. Ballintine, M.D.,
Clinical Director
Jin Kinoshita, Ph.D.
Scientific Director

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three medical staff fellows from those candidates who have completed an accredited 3-year ophthalmology program. Fellows spend time in both clinical and laboratory research including patient care activities.

In selection of medical staff fellows, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

The National Eye Institute has developed its clinical and research program into four major branches, the Laboratory of Vision Research, the Laboratory of Sensorimotor Research, the Office of Biometry and Epidemiology, and the Clinical Branch.

Office of Biometry and Epidemiology—
Fred Ederer, M.A.

The Office of Biometry and Epidemiology conducts studies that tend to fall into the broad areas of clinical trials and natural history, on the one hand, and epidemiology on the other.

The clinical trials section is now responsible for three national multiclinic trials involving vitrectomy, drugs, and photocoagulation, as treatments to prevent progression in patients with diabetic retinopathy. These studies include thousands of patients, and combine the skills of several disciplines, including clinical, statistical, and computer sciences. Data generated in these studies not only provide a base for treatment strategies, but permit investigation of the extent to which risk factors other than treatment are related to disease progression.

The epidemiology section generates data on the prevalence, incidence, and distribution of diseases of the eye. Such data are used to evaluate hypotheses on the causes of such diseases. Data sets from the Framingham Eye Study and the Health and Nutrition Examination Survey are being actively analyzed to explicate the risk factors for changes in the lens and retina. A major national study of the prevalence of visual acuity impairment and its causes will soon be under way.

Laboratory of Vision Research—
Gerald Chader, Ph.D.

The laboratory is engaged in research involving the following disciplines:

Biochemistry—This section conducts studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolism of photoreceptors are also under investigation. In addition, synthesis of sugar-containing polymers in the retina are being studied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

Experimental Embryology—This section identifies and characterizes the myriad tissue interactions that control orderly growth of the vertebrate eye and assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ.

Because most congenital defects of the eye are attributable to interference with these interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. Researchers are determining which tissues are responsive to such influences, the duration of these potencies and competencies during embryogenesis, the specificities of these interactions, and the nature of interactions which control morphogenesis.

Particular attention is being focused on newly discovered, cellfree, collagen-containing "initiator layers" which are transicntly produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of the body.

Experimental Pathology—Research being conducted in this section centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of intraocular pressure on eye tissue, the damaging effect of light on the retina, laser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

Neurophysiology—Investigations on the cellular organization underlying visual perception are currently under way in this section. Studies are being conducted on the responses of single nerve cells at various levels in the visual nervous system of mammals. The purpose of this work is to understand how nerve cells contribute to visual sensations such as color, shape, movement, and depth. The technique employs fine microelectrodes which can be inserted into the brain in order to record from single nerve cells. It uses refined optical methods to enable an experimenter to stimulate the retina with spots or slits of colored lights whose movement and shape can be quantitatively controlled. It involves electrophorescing dye into single cells whose responses have been studied and then finding these cells within the brain or retina.

By this means both structure and function of nerve cells can be correlated and the underlying circuitry of the visual system understood. This approach requires close interaction between single cell physiology and cellular anatomy at the light and electron-microscopic level.

Retinal and Corneal Metabolism—This section is investigating the function of the retina, pigment epithelium, and cornea in relation to clinical diseases such as retinitis pigmentosa and keratomalacia.

The mechanism by which visual cells detect light and produce neural messages is not known. Calcium may play a role in the process since it mimics the effects of light on the retina and is found in very high concentrations in pigment epithelium and retinal photoreceptors. Small intracellular messengers called cyclic nucleotides have also been found in extraordinarily high concentrations in retinal photoreceptors. Since light markedly affects their concentration, they, too, are probably intimately involved in the visual process. A method of injecting various substances into visual cells is now being developed to determine directly the effect of these substances on the visual process in both normal and pathologic conditions.

Studies on the synthesis and degradation of the visual protein rhodopsin have helped explain how retinal photoreceptors are renewed. Defects in this process may underlie some forms of retinal degeneration; thus, studies using dystrophic retinas of test animals are under way to compare the process of photoreceptor renewal in normal and pathologic conditions. Substances such as hormones and neurotransmitters that affect the normal growth and development of retinal cells in tissue culture are being assessed. Several have already been identified and are being further studied in relation to their role in retinal function.

Specific receptor molecules for vitamin A have been found in retina and pigment epithelium. These receptors are probably involved in the normal uptake, distribution, and retention of the vitamin in the visual system. Differences in receptor concentrations in retinas of normal humans and patients with retinitis pigmentosa have been found.

Vitamin A receptors are also present in the cornea and conjunctiva. The possible relationship of these receptors to corneal disease is being considered. Other aspects of corneal physiology, such as glutathione metabolism, are under investigation. Such studies are important not only for understanding corneal function and transparency but for improving corneal transplant and surgery techniques as well.

Laboratory of Sensorimotor Research—
Robert Wurtz, Ph.D.

This laboratory conducts research on the central neural bases of vision and eye movements in the primate, and the application of these results to clinical problems in patients with visuomotor deficits. The laboratory uses a multidisciplinary approach, availing itself of techniques of neurophysiology, neuroanatomy, experimental psychology, psychophysics, systems engineering, and computer science.

One series of projects is designed to elucidate the central neural mechanisms in the control of visually guided eye movements. The activity of single neurons in cortical and subcortical areas is recorded using microelectrodes placed in the brains of behaving animals, in order to analyze the relationship of neural events to eye movements and the presentation of visual stimuli. Quantitative studies of eye movements are performed in animals with lesions in those brain areas which physiological recordings have indicated may be important in the neural mechanisms underlying eye movement and visual perception. The anatomic connections of these areas of interest are studied using axoplasmic transport methods.

A second series of experiments investigates the visual processing underlying visual perception. These experiments correlate the discharge of single cells within cortical and subcortical regions of the brain with the stimulus presented to the monkey.

In another series of studies the vestibulo-ocular system is used as a tool to study the mechanism by which the brain can adjust to environmental changes. This adaptive plasticity is studied using systems analysis of single neuron discharge patterns recorded from performing animals, and analysis of the performance of monkeys, normal human subjects, and patients with oculomotor deficits.

The ability of patients with visuomotor deficits is studied using paradigms for performance that have been developed using normal humans and monkeys, in order to study residual abilities following damage to discrete brain areas, and to develop strategies for rehabilitation of brain-damaged patients.

Since recent advances in sensorimotor physiology and psychophysics have been made possible by developments in the application of the online laboratory computer to these problems, a significant effort in the laboratory is the development and refinement of computer methods for the control and analysis of experimental results.

Laboratory of Molecular and Developmental Biology—
Joram Piatigorsky, Ph.D.

This laboratory conducts basic research on cellular and molecular biology. Emphasis is given to molecular and developmental genetics. The research is designed to elucidate both normal and disease processes. Particular attention is given to hereditary diseases which can be studied at the gene level. Much (but not all) of the work uses eye tissue as models for general problems concerning cellular differentiation and gene expression. Normal and pathogenic visual processes are also being related to the structure and function of genes.

Three major gene families are currently being investigated; namely, crystallins, opsins, and collagens. DNA clones are being constructed, analyzed, and used as probes for understanding a variety of normal and pathogenic circumstances. Phospholipid metabolism—particularly at the cell membrane—is also under investigation in order to advance our knowledge of cellular differentiation and differential gene expression.

Clinical Branch—
Elmer J. Ballintine, M.D.

The branch plans and conducts clinical

research into the causes, prevention, diagnosis, and treatment of visual system disorders. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the branch's responsibility to investigate the causes and prevention of visual impairment.

- Cataract Section—
  Jin Kinoshita, Ph.D.

Cataracts of unusual origin and congenital cataracts are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

- Section on Neuro-opthalmology—
  David B. Cogan, M.D.

Patients from the ophthalmic and neurologic services are being studied using advanced methods for electrooculography, pupilometry, videotape recording, and computer analysis. The main emphasis of these studies is on cerebellar disorders that affect ocular movements.

- Section on Glaucoma—
  Douglas E. Gaasterland, M.D.

Intraocular fluid dynamics in normal and glaucomatous eyes and their alteration by pharmacologic agents are being studied. A controlled clinical trial to test the value of early treatment of ocular hypertension is under way. Innovative surgical techniques are being assessed in selected cases of primary, secondary, and congenital glaucoma in cases in which antiglaucoma surgery has failed. The properties of trabecular meshwork are being studied in tissue culture.

- Section on Ophthalmic Genetic Studies—
  Muriel I. Kaiser, M.D.

These include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogenesis of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

The pathogenesis of unusual types of congenital or developmental anomalies of the eye is being studied under protocol. These cases include pigment dispersion syndrome, progressive essential iris atrophy, oculocutaneous albinism, and abnormalities of the anterior chamber angle associated with glaucoma.

- Section on Retinal and Ocular Connective Tissue Diseases—
  David A. Newsome, M.D.

Retinal deteriorations—Clinical, biochemical, cell biological, and metabolic investigations are being conducted to define underlying mechanisms in diseases such as senile macular and related degenerations and the maculopathy of retinitis pigmentosa. Macular edema is also of special interest. The retinal pigment epithelium, its normal function, pathophysiology, and interrelationships are of special interest. Family studies of macular and retinal degenerations are emphasized.

Vascular diseases—Clinical investigations are being conducted in the treatment and underlying mechanisms of diabetic retinopathy.

Ocular connective tissues—Characterization and purification of extracellular matrix molecules synthesized by normal and abnormal ocular tissues, immunofluorescent antibody studies, and the enzymology and immunology of corneal melting are being investigated actively.

- Section on Ophthalmic Pathology—
  Merlyn Rodrigues, M.D., Ph.D.

Surgically excised biopsy material and eyes obtained from autopsies or enucleations performed at the Clinical Center are processed and studied by light and electron microscopy. Many of these specimens are from subjects with unusual metabolic and genetic diseases, glaucoma, and retinal disorders. Some of these specimens are further investigated by immunohistochemical techniques. The ocular effects of diabetes in animals, S-antigen uveitis, and chemotaxis induced by synthetic mediators have been studied in collaboration with investigators from other institutes at NIH. There is also opportunity for research on corneal diseases and glaucoma and for further investigation of mediators of ocular inflammation and animal models of diabetes.

A 2-year training program in clinical and experimental eye pathology is available under the supervision of Drs. Cogan, Kuwabara, and Rodrigues. This program includes experience in histochemistry and electron microscopy.

- Section on Ocular Immunology—
  Robert B. Nussenblatt, M.D.

Immunologic mechanisms relating to ocular inflammatory disease are being studied. The possible role of ocular autoimmunity in uveitis is being actively investigated. Patients with posterior uveitis, i.e., toxoplasmosis, pars planitis, birdshot choroidopathy, and sarcoid are being sought in order to evaluate their immunologic responses. The evaluation of patients with ocular inflammatory disease also includes monitoring their ocular physiologic responses during disease and when the inflammation is quiescent. The relationship of HLA and the immunologic response of patients with ocular inflammatory disease to antigens is being looked at, as are other immunologic factors, such as antibody production, suppressor cell activity, and macrophage responsiveness. Patients are in addition being sought for a controlled double masked study in the therapy of ocular toxoplasmosis.

National Heart, Lung, and Blood Institute

Claude Lenfant, M.D.,
Director
Jack Orloff, M.D.,
Director of Intramural Research
Harry R. Keiser, M.D.,
Clinical Director

Candidates for research and clinical positions as medical staff fellows have only one interview in this Institute. Medical staff fellows are interviewed by a committee made up of the director of intramural research, the clinical director, and the deputy clinical director. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the National Heart, Lung, and Blood Institute (NHLBI). After appointment and prior to entering on duty each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the fellow and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. On the basis of past experience, it appears virtually certain that each fellow will be able to work with the group of his or her choice. The level of research responsibility and freedom will depend upon the fellow's training and experience as well as desires.

Each medical staff fellow will devote time primarily to research in the laboratory under the supervision of a preceptor in the area of selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of the laboratory.

All appointments as medical staff fellow are for a minimum of 2 years with a third optional year. In the past, most fellows have elected to remain for 3 full years and have been accorded this privilege.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research. Candidates must have satisfactorily completed a minimum of 2 years of residency training in general internal medicine in a program approved by the American Board of Internal Medicine by the starting date of their appointment. The first year of the clinical fellowship will be credited as a third year of training in internal medicine by the American Board of Internal Medicine if the candidate's clinical competence was satisfactory during the previous 2 years of training and is satisfactory here.

Medical staff fellows will be responsible, under the guidance of investigators on the NHLBI staff, for the primary medical care of research patients during 10 to 12 months of the first year of their service. During this time they will rotate through the four medical services that serve the clinically oriented branches of the Institute and assist in the work of the service with consultations and in the outpatient department. These services occupy 75 beds and include cardiology, hypertension-endocrinology, lung, hematology, and metabolism.

The clinical period is one of intensive training under direction of the clinical director and staff. It offers exposure to case material of extraordinary range and to highly sophisticated approaches to investigation of disease.

The fellow devotes both time off the wards and a full 12-14 months of the 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either clinical or nonclinical.* No clinical responsibilities are required during the second or the optional third year for fellows who have chosen nonclinical laboratories.

Medical Staff Fellows in Surgery

The Surgery Branch appoints four to five fellows in surgery for a 2-year period beginning each July 1. The program is designed for young surgeons with primary interests in cardiovascular surgery and cardiovascular physiology. In making appointments, preference will be given to candidates contemplating a career in research or academic medicine. Candidates must have completed an internship and at least 1 year of surgical residency by the starting date of their appointment. Candidates interested in this possibility and desiring additional information are encouraged to write to Charles L. McIntosh, M.D., Ph.D., Acting Chief, Surgery Branch, NHLBI, Bldg. 10, Room 2N248, National Institutes of Health, Bethesda, MD 20205.

Appointments in Laboratory Research

These appointments are designed to give highly qualified physicians an opportunity to do either clinical or basic research in any area of the Institute under the direct supervision of an experienced preceptor. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises.

Staff Appointments

Laboratories with the NHLBI sometimes have openings for medical staff fellows appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Checklist for the Institute. Selections for those positions are made by the chief of the branch or laboratory.

Medical Staff Fellows in Epidemiology

The Epidemiology Branch conducts population-based studies on the occurrence and natural history of cardiovascular, cerebrovascular, blood, and obstructive pulmonary diseases in general and selected populations in the United States and foreign countries. Through clinical examinations and analyses of available data, these studies seek to improve knowledge of the personal, environmental, and familial factors underlying these disorders. One or two candidates are chosen each year for 2-year assignments in Bethesda or for one of the field programs. The fellowships may begin after internship or after 1 year of training in a clinical residency or school of public health. Interested candidates are encouraged to write to Paul Leverton, Ph.D., Acting Chief, Epidemiology Branch, NHLBI, Bethesda, MD 20205, for more detailed information about specific assignments.

Joint Endocrinology Training Program

Medical staff fellows from the NHLBI may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to quality fellows for the Endocrinology Subspecialty Boards. NHLBI participants will spend an additional 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the fellow will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the fellow's 3 years will be spent primarily in research activity within the NHLBI, although he or she will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two NHLBI fellows to enter this program in any one year.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Medical staff fellows are expected to take advantage of this academic work. (See part 4, page 127.)

Clinical Research Branches

Cardiology Branch—
Stephen E. Epstein, M.D.

- Section on Cardiovascular Diagnosis—Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by various cardioactive agents, with particular emphasis on calcium antagonists.

- Section on Experimental Physiology and Pharmacology—
Stephen E. Epstein, M.D.

Research is aimed toward understanding the physiologic, anatomic, and biochemical mechanisms responsible for control of the normal heart and circulation, elucidation of the alterations produced by ischemic and nonischemic heart disease, and evaluation of interventions designed to reverse the biochemical and, thereby, the physiologic aberrations of function. Several approaches are being employed to achieve the above, including hemodynamic, echocardiographic (one- and two-dimensional systems), and radionuclide studies in man, electron-microscopic and biochemical studies of tissues obtained from human and animal surgical specimens and pharmacological investigations in man and animals. A major interest is the study of calcium antagonist drugs.

Clinical Hematology Branch—
Arthur W. Nienhuis, M.D.

The research activities in this branch, while diverse, are generally focused on the problems of red cell production, hemoglobin synthesis, and hemoglobin function. Specific monoclonal antibodies produced by hybridoma cells are being characterized with respect to their reactivity with hematopoietic stem cells. These antibodies will be used to purify stem cells, thereby facilitating their functional and biochemical characterization and also to correlate stem cell number with function in patients with various bone marrow failure syndromes. The regulation of several globin genes is being studied in the context of developmental switches in hemoglobin phenotypes in man and other species. Furthermore, the study of gene expression in patients with thalassemia is directed toward definition of the molecular defects which result in deficient hemoglobin synthesis in these syndromes. Various strategies are being devised and tested with the long-term goal of introducing functional genes into the erythroid cells of such patients. Experimental strategies directed toward treatment of severe aplastic anemia, iron overload secondary to chronic transfusion, and sickle cell anemia are under investigation.

Hypertension-Endocrine Branch—
Harry R. Keiser, M.D.

This branch represents a merger of the former Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension; activities are wide-ranging, as indicated by the description of section activities.

- Section on Experimental Therapeutics—Harry R. Keiser, M.D.

A wide spectrum of research opportunities is offered, ranging from basic biochemistry, physiology and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of the kallikrein-kinin system, renin-angiotensin-aldosterone system, prostaglandins and catecholamines and their interactions, conducted both in man and in experimental animals. Other studies encompass disorders of serotonin, histamine, and peptides.

- Section on Biochemical Pharmacology—
Walter M. Lovenberg, Ph.D.

This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of enzymes responsible for the biosynthesis of neurohumoral amines. The role of these systems in disease states, particularly hypertension, is of prime interest, and investigations are extended from the molecular level to experimental animals and man.

Molecular Disease Branch—
H. Bryan Brewer, M.D.

The research activities of this branch are directed toward the elucidation of the molecular mechanisms involved in lipid transport and metabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis. Studies take several approaches employing protein chemistry, immunology, tissue culture, molecular biology, and enzymology. Clinical research is focused on the effects of drugs and therapeutic diets on dyslipoproteinemia and on kinetic analysis of the metabolic defects in patients with these diseases. Activities are integrated in such a way that, if medical staff fellows wish, they may participate in collaborative research involving several different areas.

Pathology Branch—
William C. Roberts, M.D.

This branch is concerned with the study of morphologic aspects of cardiovascular and pulmonary diseases and their correlation with functional derangements. Morphologic analyses include transmission and scanning electron microscopy.

Pulmonary Branch—
Ronald G. Crystal, M.D.

Research in this branch is designed to investigate the structure and function of the lung in health and disease through cellular and biochemical methods. Both laboratory and clinical investigations are conducted. Techniques of protein chemistry, molecular biology, tissue culture, and immunology are used. Emphasis is placed on the regulation of synthesis and degradation of connective tissue and on the inflammatory and immune processes in the normal and diseased lung. Clinical research is directed toward correlating physiologic, biochemical, immunologic, and morphologic observations in patients with interstitial lung disease, destructive lung disease, hereditary disorders of connective tissue, hypersensitivity lung disease, and other lung disorders with an immunologic basis.

Surgery Branch—
Charles L. McIntosh, M.D., Ph.D.,
Acting Chief
(See page 38, Medical Staff Fellows in Surgery.)

Basic Research Laboratories

- Section on Theoretical Biophysics—
  John L. Stephenson, M.D.

The primary interest of this section is the theory of transport processes in biological systems, with particular reference to problems in cardiovascular, renal, and membrane physiology. The section is concerned with the formulation of theoretical models and the development of mathematical and computational methods for their analysis. Currently, much of the research centers on the mechanism of urine formulation in the mammalian kidney and theoretical aspects of epithelial transport of electrolytes and water.

Laboratory of Biochemical Genetics—
Marshall Nirenberg, Ph.D.

- Section on Molecular Biology—
  Marshall Nirenberg, Ph.D.

This section is primarily concerned with basic biochemical studies pertaining to the transfer of genetic and neural information, for example, genetic programs for differentiation that determine informational reactions of neurons. Systems and problems involve the culture of mammalian cells and hybrid cells. Studies are also done on gene function for informational molecules such as enzymes of transmitter metabolism receptors, membrane ionophores, cyclic nucleotides, and other components required for cell recognition and communication.

- Section on Macromolecules—
  Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms. One area of interest involves the hypothalamic tripeptide thyrotropin-releasing factor. The biological properties of some new derivatives of thyrotropin-releasing factor are under investigation. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells.

Laboratory of Biochemistry—
Earl R. Stadtman, Ph.D.

- Section on Enzymes—
  Earl R. Stadtman, Ph.D.

Studies of this group are concerned with the elucidiation of various mechanisms of metabolic regulation, specifically, studies on the regulation of enzyme activities by allosteric interactions, by enzyme catalyzed covalent modification (phosphorylation, nucleotidylation, etc.) of interconvertible enzymes, and on the regulation of enzyme levels by changes in the rates of protein degradation mediated by mixed-function oxidase catalyzed inactivation of enzymes. These studies involve the isolation and characterization of key regulatory enzymes and of the enzymes which catalyze their covalent modification, oxidative inactivation, and proteolytic degradation.

- Section on Intermediary Metabolism and Bioenergetics—
  Thressa C. Stadtman, Ph.D.

This section is concerned primarily with investigations on the mechanisms of anaerobic metabolism of one-carbon compounds and amino acids and phosphorylation reactions coupled to the electron transfer processes. Emphasis is on the roles of various coenzymes (*e.g.,* vitamin B_{12} coenzyme, CoA, deazaflavins, quinones) and electron transfer proteins such as selenoproteins, molybdo-iron sulfur proteins and flavoproteins. The occurence and roles of selenium in enzymes and amino acid transfer nucleic acids are being investigated currently.

- Section on Protein Chemistry—
  Ann Ginsburg, Ph.D.

Studies on protein structure in this laboratory are directed toward understanding the roles of ligand binding and of protein-protein interactions in enzyme catalysis and regulation.

- Section on Metabolic Regulation—
  P. Boon Chock, Ph.D.

This section conducts biophysical studies on various enzymes and proteins with emphasis on the mechanisms of enzyme action and its regulation. Currently, we are investigating the roles of covalent modification in metabolic regulation of enzymes. This involves the study of the glutamine synthetase cascade and the phosphorylation/dephosphorylation cascade. In addition, we are studying the mechanism for the activation of cyclic nucleotide phosphodiesterase and calcineurin by calmodulin, enzyme-monoclonal antibody interaction, and glutamine synthetase catalysis.

Laboratory of Cell Biology—
Edward D. Korn, Ph.D.

This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

- Section on Cellular Biochemistry and Ultrastructure—
  Edward D. Korn, M.D., Ph.D.

This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the molecular and ultrastructural basis of cell motility. Cytoplasmic actin, myosin, and related proteins are purified from nonmuscle cells and their interactions studied and compared to their muscle counterparts. Currently, emphasis is on the regulation of actin polymerization, the regulation of actin-activation of myosin-ATPase, and the characterization of multiple myosins in a single cell. Opportunities are available for research and training in biochemistry and electron-microscopy.

- Section on Cellular Physiology—
  Evan Eisenberg, M.D., Ph.D.

This section conducts studies on the molecular events of muscle contraction including the interaction of actin and myosin with each other and with the control proteins, tropomyosin, and the troponins. Emphasis is on kinetic studies with pure proteins.

- Section on Membrane Enzymology—
  Richard Hendler, Ph.D.

This section studies enzyme systems that require organization on, or interaction with, membranes in order to ensure their proper functioning. The synthesis of DNA by enzyme complexes and the electron transport chain of *Escherichia coli* are presently being investigated.

- Section on Organelle Biochemistry—
  Martin Flavin, M.D., Ph.D.

This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the

physiologic regulation of assembly and function. At this time the major emphasis is on the mechanism of polymerization of microtubules in brain and unicellular organisms.

Laboratory of Cellular Metabolism—
Martha Vaughan, M.D.

- Section on Metabolic Regulation—
  Martha Vaughan, M.D.

Research concerns mechanisms of hormone action with emphasis on the enzymes involved in synthesis and degradation of cyclic nucleotides.

- Section on Biochemical Physiology—
  Vincent C. Manganiello, M.D., Ph.D.

Research is concerned with the action of certain peptide hormones, glucocorticoids, and prostaglandins on growth and function of mammalian cells, especially cultured cells.

- Section on Molecular Mechanisms—
  Joel Moss, M.D., Ph.D.

Research is concerned with the molecular basis for regulation of enzymes involved in cyclic nucleotide metabolism, e.g., subunit structure, covalent modification, and effector interactions.

Laboratory of Chemical Pharmacology—
James R. Gillette, Ph.D., Chief
Michael A. Beaven, Ph.D.
Deputy Chief

- Section on Drug-Enzyme Interaction—
  James R. Gillette, Ph.D.

The interests of this section center on various aspects of drug disposition including pharmacokinetics and the relationship between drug metabolism and drug toxicity. Its main objectives have been understanding the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

- Section on Drug-Tissue Interaction—
  Gopal Krishna, Ph.D.

This group is involved in the study of the initial events occurring in cells as the result of a variety of drug-hormone cell interactions, including the role of cyclic nucleotides as mediators of a variety of hormone actions. Recently, this section has become involved in the investigation of the biochemical mechanisms that may be involved in drug-induced tissue lesions.

- Section on Pharmacological Chemistry—Lance R. Pohl, Ph.D.

This section studies the mechanisms of metabolism, action, and toxicity of pharmacologically active chemicals. It includes studies of the identification of active substances formed in the body, the characterization and regulation of the enzymes that either produce or metabolize these agents, and the biochemical basis of their pharmacologic and toxicologic actions.

Laboratory of Chemistry—
Henry M. Fales, Ph.D.

This laboratory conducts research on methods for the structural analysis of organic compounds and investigates their biological function. Specialties are mass spectrometry, nuclear magnetic resonance, X-ray crystallography, advanced chromatography, advanced chromatographic methods, radioimmunoassay, and data retrieval techniques. Collaborative studies are carried out with other chemists, clinicians, and biologists.

- Section on Physiological Chemistry—
  John J. Pisano, Ph.D.

The Section on Physiological Chemistry studies normal and pathological states in man at the molecular level. Under investigation are biologically active peptides (vasoactive and neuroactive), precursor proteins of the peptides, and the enzymes involved in their biosynthesis and degradation. Modern analytical techniques such as gas chromatography, high-performance liquid chromatography, affinity chromatography, mass spectrometry, and radioimmunoassay are commonly employed. Research is currently directed to the study of hypertension, new factors regulating coagulation and fibrinolysis, micro methods for the detection and the amino acid sequence analysis of polypeptides, and the discovery of naturally occurring biologically active peptides using a variety of bioassay techniques.

- Section on Chemical Structure—
  Henry M. Fales, Ph.D.

This group isolates and identifies

biochemically important and structurally interesting organic compounds using gas, liquid, high-pressure, and thin-layer chromatography in conjunction with mass spectrometry, nuclear magnetic resonance, and X-ray crystallography. The section also develops and extends methodology in above fields. Typical applications include drug metabolites, acidic components of urine in diseased states, analysis of cardiovascular drugs, insect and plant toxins, and synthetic intermediates.

- Section on Structural Nuclear Magnetic Resonance—Robert H. Highet, Ph.D.

The section emphasizes the development and use of new techniques to study the structure and chemical characteristics of compounds of biological interest. The structure of metabolites of steroidal drugs and alkaloidal toxins and the factors influencing aromatic-alicyclic tautomerism are typical areas for investigation.

Laboratory of Kidney and Electrolyte Metabolism—
Maurice B. Burg, M.D.

- Section on Electrolyte Transport—Jack Orloff, M.D.
- Section on Renal Mechanisms—Maurice B. Burg, M.D.
- Section on Membrane Metabolism—Joseph S. Handler, M.D.

This laboratory conducts research on the mechanism and regulation, hormonal and otherwise, of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, and epithelial cell cultures. Electrophysiology and intermediary metabolism as related to transport are emphasized.

Laboratory on Molecular Cardiology—
Robert S. Adelstein, M.D.

Current investigations are directed toward understanding the function and regulation of contractile proteins in muscle and nonmuscle cells. The role of cyclic nucleotides, calcium, calmodulin, and myosin phosphorylation in regulating actin-myosin interaction is of particular interest. Projects include myosin phosphorylation and the regulation of kinases and phosphatases in smooth muscle, heart, and nonmuscle cells such as brain, blood platelets, and myoblasts. The role these proteins play in cellular development, differentiation, and tumorigenicity is of current interest.

Laboratory of Molecular Hematology—
W. French Anderson, M.D.

This laboratory is concerned with investigation into the mechanism and regulation of mammalian gene expression and protein synthesis. Areas of research include molecular cloning of globin and other genes, cellfree transcription of cloned genes, gene transfer of globin (and other) genes by physical microinjection and cellular transformation techniques, regulation of protein synthesis in reticulocyte lysates, studies on globin gene expression using mouse erythroleukemia cells and somatic cell hybrids. Joint studies are also carried out with the Clinical Hematology Branch.

Laboratory of Technical Development—
Robert L. Bowman, M.D.

This laboratory conducts research on instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicromethods to practical clinical instrumentation.

- Section on Biophysical Instrumentation—Robert L. Berger, Ph.D.

This section develops methods and instruments based on new physical and computer science technology to measure reaction kinetics, molecular structure, and chemistry of substances of biomedical interest. Current work involves developing calorimetric, Mossbauer spectroscopic, laser photolysis, fast spectroscopic, and fluorometric systems.

- Section on Pulmonary and Cardiac Assist Devices—
Theodor Kolobow, M.D.

This section conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This includes the development of improved blood oxygenators, blood pumps, and control systems.

National Institute on Aging

T. Franklin Williams, M.D.,
Director
Richard C. Greulich, Ph.D.,
Scientific Director
Reubin Andres, M.D.,
Clinical Director

Medical Staff Fellows

The Intramural Research Program of the National Institute on Aging (NIA) is located at the Gerontology Research Center in Baltimore, Maryland. The clinical and basic programs of the laboratory of Neurosciences is located at the NIH Clinical Center, Bethesda, Maryland.

The multidisciplinary program of the GRC, located on the campus of Baltimore City Hospitals, offers 2-year clinical and basic research training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, medical staff fellow may participate in clinical activities of Baltimore City Hospitals and the nearby Johns Hopkins Hospital. Two-year fellowship appointments may be extended in special instances to 3 years. On occasion, such extended programs, which include clinical experience, may serve to qualify the individual for certification by a subspecialty board, such as endocrinology.

In addition to the 2-year appointment limited to laboratory research at the center, there are two 3-year programs of combined clinical and research training in collaboration with the Departments of Medicine at the Johns Hopkins University and the Baltimore City Hospitals. These special programs are in cardiology and in geriatric medicine. They are offered to a limited number of candidates each year. In both programs the first year is spend in clinical training as a resident physician or clinical fellow and the second and third years are spent in clinical or laboratory research at the Gerontology Research Center.

The clinical year of the cardiology program is primarily at the Johns Hopkins. It includes training in noninvasive techniques such as radionuclide angiography and echocardiography; and in cardiac catheterization, clinical consultation services, electrophysiology laboratory, and the coronary care unit. The 2 research years are spent in the Cardiovascular Section of the Clinical Physiology Branch.

The first year of the geriatric medicine program involves clinical training primarily at the Baltimore City Hospitals. It includes rotations through an inpatient consultation service, home care program, long-term institutional care at both skilled and chronic hospital levels, rehabilitation, and ambulatory care. The subsequent 2 research years are spent in one of the clinical or basic research laboratories described below in accord with the aptitudes, experience, and career goals of the individual fellows.

Medical staff fellows are encouraged to participate in seminars conducted by the NIA center's staff who present a comprehensive view of research in aging. Weekly research conferences are presented by staff members and invited lecturers.

A primary resource for clinical investigation on human subjects is the Baltimore Longitudinal Study of Aging. The subjects are volunteers, 20 to 96 years old or more, who reside in the community, who return for extensive studies every 2 years, spend 2½ days as inpatients each visit, and are enrolled for their entire lives. The study of men is now of 25 years' duration and involves 650 active participants; the study on women began in 1978 and its size will eventually be comparable to the male sample. The female cohort currently numbers 350 women. Medical staff fellows share in the examination of these patients.

In support of its research program, the center maintains extensive animal colonies to provide rats, dogs, and rabbits of known age, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment and photography and arts services. Computer facilities are also available, and instruction in the use of computers for laboratory research is provided. The library of the center contains one of this country's most extensive collections of literature on aging research as well as standard scientific journals.

The Laboratory of Neurosciences, located at NIH's Clinical Center in Bethesda, Maryland offers 2 years of both clinical and basic research training. In addition, there is the potential for a third or fourth year of study.

Prospective candidates wishing further information should write to either Richard C. Greulich, Ph.D., Scientific Director, or Reubin Andres, M.D., Clinical Director, c/o the NIA Gerontology Research Center, Baltimore City Hospitals, 4940 Eastern Avenue, Baltimore, MD 21224. Prospective candidates wishing further information about the Laboratory of Neurosciences should write to: Neal A. Cutler, M.D., Deputy Clinical Director, NIA, Building 10, Room 10N314, Bethesda, MD 20205.

Clinical Research Branches

Clinical Physiology Branch—
Reubin Andres, M.D.

This branch is primarily concerned with studies on physiologic changes occuring over the entire adult lifespan. Studies include the quantification of age changes, elucidation of mechanisms underlying these changes, and relationships between aging processes and specific disease states.

- Endocrinology Section—
  Robert I. Gregerman, M.D.

This section conducts studies on the molecular basis of age-related changes of hormone responses, especially those related to the biochemistry of the adenylate cyclase system and hormone receptors; aging and the endocrinology of the reproductive system; and the enzymology and peptide chemistry of the renin-angiotensin system. Clinical studies are conducted on subjects from the Baltimore Longitudinal Study of Human Aging. Studies on rodents are done on a variety of organs; hormone studies are done in animals of all ages.

- Cardiovascular Section—
  Edward G. Lakatta, M.D.

Scientists in this section investigate cardiovascular hemodynamic function in man using noninvasive methods that include studies both in normal and cardiovascular disease states. Studies on isolated cardiac muscle focus on the mechanisms that govern excitation-contraction coupling. Additional studies investigate the effect of age, hypertrophy, and physical conditioning on electrophysiological, contractile, and biochemical parameters in cardiac muscle. Response to stress such as hypoxia and adrenergic stimulation and other pharmacological interventions are also studied in these animal models.

- Metabolism Section—
  Reubin Andres, M.D.

This section emphasizes research on glucose homeostasis and its endocrine control. Factors controlling insulin secretion, including gastrointestinal insulinotropic hormone, are quantified with the use of servo-control glucose clamp technique. Clinical investigations in man are concerned with the assessment of interrelations among such variables as age, obesity, diabetes mellitus and its complications, serum lipids, dietary factors, and physical activity. Biologic rates of aging in multiple systems are also assessed. The isolated perfused rat pancreas preparation supplements human studies.

- Clinical Immunology Section—
  William H. Adler, M.D.

Studies are conducted on the decline in host immune responsiveness that is seen in aging. These studies involve the development of diagnostic procedures for the detection of relative immunodeficiencies in humans and the investigations of the mechanisms of these deficiencies in humans and experimental animals.

- Human Performance Section—
  Jordan D. Tobin, M.D.

This section supports the Baltimore Longitudinal Study of Human Aging with work in a variety of areas. Body composition studies seek the causes of tissue loss in the aged. Exercise physiology research is designed to determine the causes of reduced physical capacity in old age. Habitual physical activity and nutrition of subjects are monitored. Assessments are made of neuromuscular function, psychomotor capacity, hearing, and vision. Pulmonary physiology is studied in the context of genetic and environmental factors. Other work includes studies of the relationship of blood pressure to psychomotor variables and intelligence; dermatoglyphics in disease, world populations, twins, and aging; and the factors underlying reduced sexual function in the elderly.

Laboratory of Neurosciences—
Stanley I. Rapoport, M.D.

The laboratory's clinical program investigates cerebral metabolism in man in relation to aging and dementia. The laboratory also examines pharmacokinetics and peripheral metabolism of centrally acting drugs as a function of age.

- Brain Aging and Dementia Section—
  Neal R. Cutler, M.D.

At NIA's Section on Brain Aging and Dementia, located at the Clinical Center of the National Institutes of Health in Bethesda, MD, clinical scientists are involved in research activities focused primarily on dementias and associated neuropathologic diseases as these relate to the elderly. Studies look closely at multi-infarct, Alzheimer's type senile dementia, and Parkinson's disease. The section also examines the normal aging process from a biochemical, cardiovascular, and general physiologic perspective which includes a careful evaluation of brain function. The newest technologies, such as positron emission tomography (PET), are employed to look at brain metabolism in aging and dementia.

Particular attention is paid to the careful clinical evaluation of the noradrenergic and dopaminergic systems, through the use of biochemical and pharmacological explorations, in the areas of normal aging, essential hypertension, and related disorders.

The clinical pharmacology of aging is another major area of interest for our clinical program and includes the careful evaluation of the pharmacokinetics and pharmacodynamics of various antihypertensive and central nervous system agents in the elderly.

In addition, there is a major interdigitation between basic laboratory investigations of cerebral metabolism and neuropharmacology.

Basic Research Laboratories

Office of the Scientific Director—
Richard C. Greulich, Ph.D.

- Comparative Nutrition Section—
  Charles H. Barrows, Sc.D.

Scientists investigate the relationship between aging and nutrition in animal populations. The specific areas studied include the effects of age on absorption, distribution, and utilization of known nutrients and the mechanisms responsible for an increased lifespan associated with dietary restriction. These investigations are done with physiologic, biochemical, and electronmicroscopic techniques. Other studies deal with comparative mammalian biochemistry including investigations of the stability of gene control mechanisms and the characterization of chromatin.

- Experimental Morphology Section—
  Richard C. Greulich, Ph.D.

This section brings the most modern techniques of microscopy (TEM, SEM) and the related techniques of high resolution autoradiography and electron and X-ray probe microanalysis to bear on problems of structural-functional relationships during aging. Current interests include cell-cell interactions, junctional complexes, and epidermal aging.

Laboratory of Behavioral Sciences—
Bernard T. Engel, Ph.D.

- Psychophysiology Section—
  Bernard T. Engel, Ph.D.

This laboratory is primarily concerned with the application of behavioral and psychological techniques and principles to the control or mediation of physiologic responses. There are both clinical research programs in the area of behavioral medicine and basic research programs using animal models to study neural control of cardiovascular function, as well as central neurotransmitter changes with age.

- Learning and Problem-Solving Section—David L. Arenberg, Ph.D.

This section investigates the effects of aging on motor behavior, perceptual skills, learning, memory, and problem-solving ability. Laboratory facilities exist to measure cognitive and perceptual function in man, in addition to learning and motor behavior in rodents (including selected inbred strains of mice).

- Stress and Coping Section—
  Paul T. Costa, Jr., Ph.D.

Investigators in this section examine personality and its influence on life-course patterns including health behaviors, career, family and leisure adjustment, and coping with life stresses. Research emphasizes individual assessment of behavior and personality and their relationship to a wide variety of outcomes. Longitudinal and multivariate approaches are used to evaluate predictors of psychological well-being and overall quality of life.

Laboratory of Cellular and Molecular Biology—
Gunther L. Eichhorn, Ph.D.

This laboratory conducts research basic to the aging process at the cellular and molecular levels, with emphasis on genetic information transfer. Highly qualified fellows have the opportunity to become familiar with the latest techniques for the solution of biological problems at the cellular and molecular level: NMR, CD, etc.

- Inorganic Biochemistry Section—
  Gunther L. Eichhorn, Ph.D.

This section studies the effects of metal ions on nucleic acid structure and on genetic information transfer, including chromatin structure and RNA synthesis. It is primarily concerned with the mechanisms of introducing error into genetic information transfer. NMR techniques are used to study age changes in cells and animals.

- Cellular Aging and Genetics Section—
  Gunther L. Eichhorn, Ph.D.

Studies are carried out on the effect of metal ions on the viability of cells, and how they influence DNA synthesis and repair.

- Macromolecular Chemistry Section—
  Josef Pitha, Ph.D.

Scientists in this section study the interaction of cells with synthetic macromolecules. Investigators probe age changes on the cell surface with specially designed macromolecules and also synthesize potential polymeric drugs.

Laboratory of Molecular Aging—
Bertram Sactor, Ph.D.

In this laboratory, highly qualified medical staff fellows have the opportunity to develop expertise preparing them for careers in basic medical research. The thrust of the biochemical, biophysical, and physiologic programs are directed toward the biology of membranes and cells (isolated and cultured). The studies encompass calcium and phosphorus homeostasis, salt/water balance, acid/base status, and other ion and protein transport systems in the kidney, GI tract, bone, heart, and parotid gland, and examine the mechanisms by which these systems are perturbed by various pathophysiological states, including aging. The problems and questions relate to: the molecular organization of the membrane; mechanisms of vectorial transport; hormonal and vitamin D_3 metabolite regulation of transport; altered transports in animal models for specific diseases and disturbances; isolation of carriers and reconstruction of functional synthetic membranes; alterations in the molecular conformation and function of membrane proteins with age utilizing monoclonal antibody technology; the turnover of proteins and lipids in membranes; and the failure to maintain membrane structure and function with age which leads to physiologic dysfunction and cell death.

- Intermediary Metabolism Section—
  Bertram Sactor, Ph.D.
- Biophysics Section—
  Bertram Sactor, Ph.D.

Laboratory of Neurosciences—
Stanley I. Rapoport, M.D.

This laboratory investigates the function, structure, physiology, biochemistry, and pharmacology of central and peripheral nervous systems and of muscle, and the changes that take place during development and aging in animal models and in man.

- Cerebral Physiology and Metabolism Section—
  Stanley I. Rapoport, M.D.

This section is located at the Clinical Center of the National Institutes of Health in Bethesda, Maryland. Scientists in this section study the untrastructure, transport, and permeability at the blood-brain barrier, blood-ocular barriers, and peripheral nerves; experimental modifications of barrier permeability; regional cerebral metabolism and blood flow in relation to brain function; neuropharmacology in relation to stress, hypertension, and synaptic transmission; neurophysiology of nerve, muscle, and synapses; and factors regulating neuronal death and neuron-neuron and neuron-effector organ interaction and neuroendocrinology. The basic program is coordinated with the clinical research program on cerebral metabolism in aging and dementia.

National Institute on Alcohol Abuse and Alcoholism

Alcohol, Drug Abuse, and Mental Health Administration

William Mayer, M.D.
Acting Director
Laura Rosenthal
Deputy Director of Intramural Research
Markku Linnoila, M.D., Ph.D.
Clinical Director

The National Institute on Alcohol Abuse and Alcoholism conducts an intramural program of basic and applied research on the multiple determinants and processes of alcoholism and other alcohol-derived health problems. The clinical facilities are located at the National Institutes of Health Clinical Center in Bethesda, Maryland; the research laboratories are located at the Flow Building in Rockville, Maryland (approximately 15 minutes from NIH), and at the NIH. Medical staff fellow appointments are available to conduct clinical and/or basic research investigations. Depending upon the appointment, certain fellows will also have clinical responsibilities.

Appointments in Clinical Research

Medical staff fellowship positions are available in neurology, internal medicine, psychiatry, experimental therapeutics, and developmental neurology. Fellows are appointed for 2 years with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on the NIAAA ward and involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NIAAA research emphases.

Candidates requiring further information about the clinical positions for medical staff fellows should write to Markku Linnoila, M.D., Ph.D., Clinical Director, DICBR, National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3C118, National Institutes of Health, Bethesda, Maryland 20205.

Appointments in Laboratory Research

NIAAA medical staff fellow positions are available for laboratory research in the Laboratory of Clinical Studies, Laboratory of Metabolism, and the Laboratory of Preclinical Studies. Appointments are for a 2-year period, with the possibility of extension.

Fellows will engage in research on contemporary biomedical problems. During their tenure, fellows will devote the larger portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities.

Research experience is gained through the process of personal guidance by senior scientists who are preceptors. Areas of study are developed by each fellow in conjunction with the preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned.

Medical staff fellows have the opportunity to work closely with a diverse group of senior investigators, to participate in courses, conferences and seminars, and to employ advanced research methodologies in the course of their research.

For further information on the NIAAA Medical Staff Fellowship Program, write to the Deputy Director, Intramural Research Program, National Institute on Alcohol Abuse and Alcoholism, 12501 Washington Avenue, Rockville, MD 20852.

Laboratory of Clinical Studies—
Markku Linnoila, M.D., Ph.D.

The major research interests of the laboratory concern effects of acute and chronic consumption of alcohol in humans. Furthermore, blood relatives of alcoholics at a high risk of developing alcoholism will be compared to age and sex matched subjects without a family history of excessive drinking or alcoholism. The general areas of inquiry are broadly defined by the names of the sections and units in the laboratory: Section of Clinical Science (Peter R. Martin, M.D.); Section of Clinical Brain Research (Michael Eckardt, Ph.D.); Section of Clinical Biochemistry and Pharmacology (Ralph Ryback, M.D.); Section of Analytical Biochemistry (Norman Salem, Ph.D.); Section of Neuroscience (Markku Linnoila, M.D., Ph.D.); Unit of Genetic Studies (David Goldman, M.D.); and the Unit of Family Studies (Yolande Davenport, M.S.W.). The techniques available include EEG-telemetry, sleep recording, activity and temperature monitoring, evoked responses, brain imaging, neuropsychological testing, advanced computer analyses of blood chemistry profiles, drug concentration measurements with liquid chromatography, monoamine and neuropeptide analyses with liquid chromatography, membrane lipid analyses with mass fragmentography, receptor studies, and animal behavioral pharmacology. The aims of the program are to test and develop new approaches for the treatment and prevention of alcoholism and its complications as well as to train professionals to work successfully in the field of alcohol research.

Laboratory of Metabolism—
Richard Veech, M.D., D.Sc.

The Laboratory of Metabolism conducts studies in basic biochemistry, clinical metabolic studies on patient samples, genetic studies with fibroblasts, and molecular biology, including studies with recombinant DNA and peptide synthesis. The aim is to provide the most appropriate tehcniques to solve the particular problem at hand.

The basic biomedical studies include the kinetics of alcohol dehydrogenase, PPi-PFK microsomal monooxygenases and the PRPP phosphoribosyl phosphotransferases. Thermodynamic studies are under way covering a number of areas including the purine salvage pathway and the carbonylphosphate synthase reaction. Metabolic studies defining the control points switching amino acids from ureagenesis to protein synthesis are under way as are studies involving glycogen synthesis, c-AMP and Co effects as well as certain metabolic inhibitors' effects on mitochondrial shuttles. Blood samples from alcoholic patients are examined to determine the nature and source of abnormal metabolites found and the contribution that genetic versus induced enzymatic changes play in inducing these abnormalities. The question is pursued further using cultured fibroblasts from alcoholic and non-alcoholic subjects as well as individuals with a variety of other known genetic diseases.

Finally, peptide fragments and analogues for various pituitary peptides are being synthesized from c-DNA fragmens and by solid state peptide synthesizer and are being tested for biological activity.

Laboratory of Preclinical Studies—
Forrest F. Weight, M.D.

A broad program of investigation is conducted on physiological, pharmacological, and chemical properties of nervous tissue and the relationship of these properties to the functional activity of the nervous system. Current experimental studies involve two main areas: (1) the physiology and pharmacology of neurons and synapses in the central and peripheral nervous system; and (2) the molecular mechanisms involved in regulating neuronal excitability and membrane permeability in nervous tissue.

Studies on the physiology and pharmacology of neurons and synapses involve primarily electrophysiological techniques such as current-, voltage-, and patch-clamp methods to study the regulation of neuronal excitability and the ionic basis of membrane permeability changes involved in drug and transmitter actions. The general areas studied include: cellular mechanisms regulating membrane excitability; cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin and GABA; membrane mechanisms of neurotransmitter, neurohormone and drug actions; cellular actions of enkephalin, endorphin and other neuropeptides; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbituates, opiates, and other neuroactive substances. Studies are performed primarily on *in vitro* preparations such as CNS slice, sympathetic ganglia, and tissue culture.

Studies of the molecular mechanisms involved in regulating neuronal excitability and membrane permeability employ physical techniques such as fluorescence absorption, polarization and lifetime, and biochemical methods such as gel electrophoresis, column chromatography, ligand binding, and high-voltage electrophoresis to identify, purify, characterize, and study membrane proteins. Studies include investigations on the role of protein phosphorylation, calcium ions, and cyclic nucleotides in the regulation of membrane properties.

National Institute of Allergy and Infectious Diseases

Richard M. Krause, M.D.,
Director
Kenneth W. Sell, M.D., Ph.D.,
Scientific Director
Michael M. Frank, M.D.,
Clinical Director

The National Institute of Allergy and Infectious Diseases (NIAID) annually appoints medical staff fellows for the laboratories described below. Fellows are selected by the clinical director, appointed to the Laboratory of Clinical Investigation, and begin after at least 1 year of residency training. Medical staff fellowship appointments in the other laboratories may begin after internship or residency training. In general, appointments to the Laboratory of Clinical Investigation carry responsibility for patients in the research program but are not otherwise different from those which begin after internship.

Specific answers to any questions or additional information may be obtained by applicants from the Scientific Director, NIAID, National Institutes of Health, Bethesda, MD 20205. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests and information desired.

Clinical Branches

Laboratory of Clinical Investigation—
Michael M. Frank, M.D.
Laboratory of Immunoregulation—
Anthony S. Fauci, M.D.

The NIAID appoints about 9 medical staff fellows. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned primary clinical responsibilities are made during the second or third year except as directed by the needs of the fellows' research.

There are 52 research beds. Medical staff fellows consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each fellow selects an area of investigative interest under the general preceptorship of the clinical director and the senior members of the staff of the Laboratory of Clinical Investigation or the Laboratory of Immunoregulation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in clinical investigation. Depending upon the area in which the medical staff fellow works, the subspecialty boards in infectious diseases or allergy-clinical immunology will usually credit the training received towards admission to these board examinations. Two to three staff fellows will be assigned to the Laboratory of Immunoregulation and six to seven to the Laboratory of Clinical Investigation.

Opportunities exist for research in a wide variety of areas of infectious, allergic, and immunological disease. Examples of studies now in progress are:

- The etiology, pathogenesis, and treatment of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases and vasculitis.
- Pathophysiology and treatment of autoimmune hemolytic anemia.
- Pathophysiology and treatment of hereditary angioedema.
- The pathophysiology and host defense response to bacteremia.
- Etiology and pathogenesis of the idiopathic hypereosinophilic syndrome.

- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- Mechanisms of regulation of immune reactivity in normal individuals and in patients with immunologically mediated diseases.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The biochemical, neurophysiologic, and immunologic abnormalities of asthma and allergic diseases.
- The role of immune complexes in the production of disease.
- Immunopathologic mechanisms in parasitic infections.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Laboratory and clinical evaluation of antiviral substances.

Further information can be obtained if inquiries with specific questions are addressed to Kenneth W. Sell, M.D., Ph.D., Scientific Director.

Research Areas and Senior Staff
Allergic Diseases—
Michael A. Kaliner, M.D., and
Dean Metcalfe, M.D.
Bacterial Diseases—
John I. Gallin, M.D.
Clinical Immunology—
Michael M. Frank, M.D.,
Eric Brown, M.D., and
Keith Joiner, M.D.
Clinical Mycology—
John E. Bennett, M.D.
Clinical Parasitology—
Franklin A. Neva, M.D.,
Eric A. Ottesen, M.D., and
Theodore Nash, M.D.
Immunoregulation—
Anthony S. Fauci, M.D.
Medical Virology—
Stephen Straus, M.D.

Basic Research Laboratories

Laboratory of Viral Diseases—
Wallace P. Rowe, M.D.

This group of scientists conducts research on the basic biology and ecology of chronic and persistent virus infections, with particular emphasis on oncogenic viruses.

This laboratory focuses on the biology of murine leukemia viruses. The genetics of transmission and expression of endogenous viral genomes, the biochemical nature of complete and incomplete endogenous viral genomes, and their role in tumorigenesis in the mouse constitute major areas of research.

These studies include investigations of the interactions between defective and competent viruses, the natural history and epidemiology of tumor viruses, genetic transmission of leukemia viruses in mice, and the viral and host genetic factors of importance in viral tumorigenesis.

Research Areas and Senior Staff
Leukemia Viruses—
Wallace P. Rowe, M.D., and
Janet W. Hartley, Ph.D.
Viral Immunology—
Herbert C. Morse, III, M.D.

Laboratory of Biology of Viruses—
Norman P. Salzman, Ph.D.

The investigations in this laboratory are primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein, and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for medical staff fellows is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology, and medicine.

Research Areas and Senior Staff
Biochemical Virology—
Norman P. Salzman, Ph.D.
Macromolecular Biology—
Bernard Moss, M.D., Ph.D.
Molecular Structure—
James A. Rose, M.D.

Laboratory of Infectious Diseases—
Robert M. Chanock, M.D.

This laboratory's activities are concerned with the basic behavior of viral and mycoplasmal pathogens that play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract and gastrointestinal tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as coronaviruses, acute gastroenteritis viruses, and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycoplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff
Epidemiology—
Albert Z. Kapikian, M.D.
Hepatitis Virus—
Robert H. Purcell, M.D.
Molecular Viral Biology—
Ching-Juh Lai, Ph.D.
Respiratory Viruses—
Robert M. Chanock, M.D.

Laboratory of Immunogenetics—
Thomas J. Kindt, Ph.D.

This group is involved in basic research on major gene complexes involved in immune function. The approaches used in these studies emphasize structural, serologic, and genetic investigations. The techniques used include quantitative radioimmunoassays, protein structure determinations, recombinant DNA technologies including gene cloning and nucleotide sequencing, preparation and study of T- and B-cell hybridomas, and a variety of immunologic assays for cellular and humoral components of the immune response.

Areas of active investigation include: studies on cloning, sequencing, and genetic analyses of genes for rabbit immunoglobulins and MHC products; structural and functional studies on murine H-2 antigens and human HLA antigens with emphasis on the D/DR complex; regulation of immunoglobulin gene expression during maturation of lymphocytes; use of hybridoma antibodies to investigate components of lymphoid cell membranes; and evaluation of the role of the MHC in the control of responses to individual antigens or infectious agents.

The opportunity is available for medical staff fellows to study in any of these areas under the preceptorship of a senior laboratory member. During their tenure, appointees become proficient in modern techniques of structural biochemistry and molecular biology and in quantitative and qualitative immunologic procedures. In addition, they gain an understanding of the genetic mechanisms underlying the ability to mount an immune response.

Research Areas and Senior Staff
Immunoglobulin Genetics—
T. K. Kindt, Ph.D., and
J. A. Sogn, Ph.D.
Membrane Antigens—
J. E. Coligan, Ph.D.
Immunobiology—
K. W. Sell, M.D., Ph.D.
Molecular Immunogenetics—
E. E. Max, M.D., Ph.D.

Laboratory of Immunology—
William E. Paul, M.D.

This laboratory is engaged in the study of various aspects of cellular immunology, immunogenetics, and immunochemistry, particularly as they bear on a fuller understanding of the biological significance of the immune response and on the role of immune mechanisms in the prevention and pathogenesis of human disease.

Areas of active investigation include the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic and idiotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells. Studies of the role of different lymphocyte classes in many human diseases are under way, and models for the study of cellular immune responses in tumor immunity are being developed. Utilization of many modern techniques in the study of immune responses will be made, including production and use of monoclonal antibodies, cloning and long-term growth of B- and T-lymphocyte lines, and molecular genetic analysis of cells of the immune system. Medical staff fellows will have the opportunity to participate in studies in one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff
Cellular Immunology and Genetic Regulation of the Immune Response—
Ira Green, M.D., William E. Paul, M.D.,
Ronald H. Schwartz, M.D., Ph.D., and
Ethan H. Shevach, M.D.
Molecular Immunology and Immunogenetics—
Ronald N. Germains, M.D., and
Rose G. Mage, Ph.D.

Laboratory of Microbial Immunity—
Richard Asofsky, M.D.

The laboratory is primarily concerned with the elucidation of basic mechanisms involved in both the cellular and humoral immune responses to microbial and tissue antigens.

Several major areas of investigation, each employing a wide variety of immunologic methods, offer the medical staff fellows comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. The significance of interaction among different kinds of lymphoid cells in the induction and manifestation of immunity is being studied in graft-versus-host reactions and in humoral immune responses. The development, distribution, and susceptibility of the interacting components to various treatments that suppress or amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations.

Autoimmune phenomena are studied using immune complex nephritis and autoimmune encephalomyelitis as models. Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. The relationship of this disease to the presence and activity of such integrated viruses as the murine leukemia agents are studied. The nature of the immune response to protozoal parasites, including the antigenic and genetic requirements for the expression of this immunity, are studied. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

Research Areas and Senior Staff

Experimental Pathology—
Richard Asofsky, M.D., and
Thomas Chused, M.D.
Microbiology and Immunology—
Phillip J. Baker, Ph.D.

Laboratory of Parasitic Diseases—
Franklin A. Neva, M.D.

This group of scientists is engaged in both basic and applied studies of parasitic diseases, with emphasis on those affecting man. A variety of protozoan (malaria, trypanosomes, giardia, leishmania, amebae, and toxoplasma) and helminth (schistosomes, filaria, and strongyloides) parasites are used for experimental work. Current studies include comparative mechanisms of energy transfer, ultrastructure of parasites, and host-parasite interactions *in vitro* and *in vivo*.

Increasing emphasis is being devoted to the immunologic response of the host in parasitic infections, both humoral and cellular. Another area of emphasis concerns the biochemical and immunologic characteristics of parasite surfaces and their interactions with the host cell membrane. Some experimental infections such as leishmaniasis, amebiasis, schistosomiasis, and filiarisis in animals are used as models of naturally occurring disease in man. The availability of different species of human as well as simian malaria parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate, certain problems that can only be investigated in the field are studied in collaboration with institutions overseas. Clinical investigators from the Laboratory of Parasitic Diseases are associated with the Laboratory of Clinical Investigation within the Section of Clinical Parasitology. Thus, selected patients are seen and studied as inpatients or outpatients at the Clinical Center.

Within limits of space and available guidance by a member of the senior staff, medical staff fellows can select their area of work and a preceptor. In addition, an organized program provides medical staff fellows with an exposure to clinical parasitology.

Research Areas and Senior Staff

Host-Parasite Relations—
A. W. Cheever, M.D.
Cell Biology and Immunology—
F. A. Sher, Ph.D.
Clinical Parasitology—
F. A. Neva, M.D.,
T. E. Nash, M.D., and
E. A. Ottesen, M.D.
Malaria—L. H. Miller, M.D.
Parasite Growth and Differentiation—
L. S. Diamond, Ph.D.
Physiology and Biochemistry—
E. C. Weinbach, Ph.D.

Laboratory of Molecular Microbiology—
Malcolm A. Martin, M.D.

This laboratory uses molecular biological techniques to study microorganisms and their capacity to produce disease in vertebrate hosts. Of prime importance is the biochemical characterization of viral, bacterial, and plasmid genomes and the detailed analysis of DNA segments that regulate the expression of specific gene products.

Programs involving DNA and RNA tumor viruses focus on those portions of the viral genome that encode proteins that initiate and/or maintain the transformed state. The roles of the host cell genetic apparatus and the immunologic system in augmenting the effect(s) of specific viral gene products during oncogenesis are also investigated. Other programs investigate the process of bacterial transformation with special emphasis on the role of plasmids in transferring genetic information from one organism to another.

Biochemical and biophysical techniques, such as molecular cloning, nucleic acid hybridization, and DNA sequencing, are used in combination with procedures such as monoclonal antibody production and immunoprecipitation to answer basic questions involving the structure and function of prokaryotic and eukaryotic genes.

Research Areas and Senior Staff
Biochemical Virology—
Malcolm A. Martin, M.D., and
Mark A. Israel, M.D.
Viral Biology—
Kenneth Takemoto, Ph.D., and
Andrew Lewis, M.D.
Bacterial Virulence—
Donald LeBlanc, Ph.D.
Mycoplasma—
Joseph G. Tully, Ph.D.

Rocky Mountain Laboratories— The Rocky Mountain Laboratories, located at Hamilton, Montana, consist of the following:

Laboratory of Persistent Viral Diseases—Bruce W. Chesebro, M.D.

This group is concerned with studies of virus-host interaction with the primary aim of elucidating mechanisms involved in establishment, maintenance, and elimination of persistent viral infections. Investigations are also made on involvement of persistent virus infection and autoimmune and immune complex diseases. Appropriate models being examined include rabies virus, scrapie, murine leukemia viruses, and Aleutian disease virus of mink.

Research Areas and Senior Staff
Murine Leukemia Viruses—
Bruce Chesebro, M.D., and
John Portis, M.D.
Aleutian Disease Virus—
Marshall Bloom, M.D.
Scrapie—
Richard Race, D.V.M.
Rabies—
Donald Lodmell, Ph.D.
Immunology—
John Coe, M.D.

Laboratory of Microbial Structure and Function—John Swanson, M.D.

Bacteria pathogenic for man are the major topics for study in this laboratory. Special attention is paid to surface components of selected bacteria, rickettsiae, mycoplasmas, and chlamydiae that relate to the virulence and/or pathogenicity of these organisms. In addition to biochemical and immunochemical studies of these organisms' surface constituents, current studies also include investigation of the metabolic capabilities and characteristics of selected rickettsial agents, toxin and other products of staphylococci and *Bordetella pertussis,* and genetic control or expression of these bacterial elements. The general goal of these studies is to document, characterize, and understand interactions between pathogenic prokaryotes and cellular or humoral components of the infected host so mechanisms of pathogenicity and virulence can be elucidated.

Research Areas and Staff—
Borrelia—
Alan Barbour, M.D.
Chlamydia—Harlan Caldwell, Ph.D.
Gonococci—
John Swanson, M.D.
Rickettsiae—
Jim Williams, Ph.D.

Epidemiology Branch—
Willy Burgdorfer, Ph.D.

The staff of this branch plans and conducts epidemiologic investigations and studies on natural histories of human diseases. One research group performs surveillance of arthropod-borne agents of human disease importance. Another group undertakes detailed histopathologic investigations of naturally occurring diseases in animals, naturally occurring slow viral diseases of animals, and infectious problems in animal models which may be related to findings in counterpart diseases of man.

Research Areas and Senior Staff
Arthropod-borne Diseases—
Willy Burgdorfer, Ph.D.
Histopathology—
William Hadlow, D.V.M.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Lester B. Salans, M.D.,
Director
Joseph E. Rall, M.D., Ph.D.,
Director of Intramural Research
Phillip Gorden, M.D.,
Clinical Director

Appointments in Clinical Research

Each medical staff fellow is assigned to one of the Institute's clinical branches or sections, within which he or she carries out both clinical work and laboratory studies. The fellow is, in effect, an apprentice investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The fellow is encouraged to choose his or her own problem for independent investigation, if facilities required for its successful pursuit and if technical advice and supervision necessary are available. In addition, the fellow provides professional care for research patients admitted to the service of the branch chief and assists in the outpatient department. There is considerable variation among the branches of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) with respect to the proportion of the fellow's time required for patient care activities.

Medical staff fellows of the Clinical Endocrinology, Diabetes, and Metabolic Disease branches participate in a 3-year Interinstitute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIADDK fellows may spend a third year in the Endocrinology Program.

The Institute recruits about 10 new medical staff fellows each year. The assignments are for 2 or 3 years and usually are not extended. One year of internship and at least one year of residency should generally be completed before the appointment begins.

Vacancies do not necessarily occur within each program each year; the Program Area Selection Checklist indicates the positions to be filled. The chiefs of branches or sections with openings and the clinical director screen applications and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical research branches are listed below with the names of the permanent investigators and a brief sketch of the areas of interest. Prospective applicants desiring more information should write to Phillip Gorden, M.D., Clinical Director, NIADDK, Building 10, Room 9N222, National Institutes of Health, Bethesda, MD 20205. Supplementary information sheets on each branch, together with selected bibliographic citations are available on request.

Appointments in Laboratory Research

NIADDK has four positions in laboratory research available each year for medical staff fellows. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During their stay here, fellows will devote the larger part of their time to laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should candidates elect a clinical area, they would not participate in clinical care of patients. The medical staff fellow, approximately 1 year prior to beginning, will visit NIADDK to select the laboratory and preceptor with whom he or she wishes to work. Candidates desiring further information about the laboratories, staffs, and bibliography can obtain this by writing J. E. Rall, M.D., Ph.D., Director of Intramural Research, NIADDK, National Institutes of Health, Bethesda, MD 20205.

Medical Staff Fellows in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment for studying the epidemiology of chronic disease such as diabetes and arthritis among the Pima Indians of Arizona. In addition, clinical research opportunities in the causes, complications, and treatment of diabetes are available at the Phoenix Clinical Research Section in the Phoenix Indian Medical Center. Candidates occasionally begin this fellowship upon completion of an internship but, in most cases, most postdoctoral training has been completed. Candidates interested in clinical research are encouraged to write to Clifton Bogardus, M.D., Phoenix Clinical Research Section, 4212 N. 16th Street, Phoenix, Arizona 85016. Those interested in epidemiology should write Peter H. Bennett, M.D., Epidemiology and Field Studies Branch, NIADDK, 1550 E. Indian School Road, Phoenix, Arizona 85014, for more detailed information.

Clinical Research Branches

Arthritis and Rheumatism Branch—
John L. Decker, M.D.

- Section on Connective Tissue Disease—John L. Decker, M.D., James E. Balow, M.D., John H. Klippel, M.D., Paul H. Plotz, M.D., and Ronald L. Wilder, M.D., Ph.D.

The pathogenesis of systemic lupus erythematosus and rheumatoid arthritis is under study both in patients with those diseases and animal models. The role of immune complexes, reticuloendothelial function, *in vitro* and *in vivo* lymphocyte and monocyte function, and various other aspects related to the immunopathogenesis of these diseases are under active study. Clinical work is related to the development of new forms of treatment of lupus, especially with nephritis, and severe rheumatoid arthritis, including new pharmacologic and cytopheretic techniques.

- Section on Cellular Immunology—Alfred D. Steinberg, M.D.

The section conducts studies on the genetic and immune bases for autoimmune diseases in mice and humans with emphasis on systemic lupus erythematosus.

- Section on Chemical Immunology—
  Henry Metzger, M.D., and
  Chaviva Isersky-Carter, Ph.D.

The section is involved in fundamental research on the structure and mechanism of immunoglobulins and their receptors on cells, using protein chemistry, immunochemistry, tissue culture, and electron microscopy techniques.

Clinical Endocrinology Branch—
Jacob Robbins, M.D., Jan Wolff, M.D., Ph.D., Saul Rosen, M.D., Ph.D., Harold Edelhoch, Ph.D., and Bruce Weintraub, M.D.

Activities in this branch range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid and polypeptide hormones. Laboratory research encompasses fundamental and applied protein chemistry, including studies on hormone transport proteins and polypeptide hormones, the mechanism of hormone actions, control mechanisms in secretory cells, adenylate cyclase-receptor interactions and membrane biochemistry, and the biosynthesis of polypeptide hormones.

Clinical Hematology Branch—
N. Raphael Shulman, M.D.

Laboratory work concerns problems in the fields of immunohematology, platelet physiology and metabolism, and blood coagulation. Current interests include mechanisms of immune platelet injury involving drug-, allo-, and so-called autoantibodies, correlation of platelet metabolism and membrane reactions with function, and interrelationships between cellular and humoral factors in hemostasis. Clinical work involves patients with immunologic and hemorrhagic disorders relevant to laboratory studies.

Diabetes Branch—
Jesse Roth, M.D., and Phillip Gorden, M.D.

The Diabetes Branch studies receptors for peptide hormones, especially insulin, insulin-like growth factors, and growth hormone. Current projects are focused on the role of receptors in disease states, receptor antibodies, and genetic disorders of glucose metabolism, isolation and characterization of receptor components, the role of receptors in hormone and drug action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects include insulin and insulin receptors in the central nervous system; the evolutionary origin of insulin, somatostatin, an other peptide messenger molecules; and their role in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

Digestive Diseases Branch—

- Section on Gastroenterology—
  Jerry D. Gardner, M.D., and
  Robert T. Jensen, M.D.

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive and immunologic processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology, biochemistry, and immunology.

- Liver Diseases Section—
  E. Anthony Jones, M.D., and
  Jay H. Hoofnagle, M.D.

Programs are concerned with research into hepatic physiology, immunology, and disease. Laboratory research projects include studies of cellular immunology and the modulation of immune responses in primary biliary cirrhosis and other chronic liver diseases; investigations of the significance of various viral antigens and antibodies in chronic type B hepatitis, characterization of cell-surface receptors on isolated hepatocytes, Kupffer cells, and hepatic endothelial cells; and the evaluation of the pathogenetic mechanisms that mediate the encephalopathy in an animal model of fulminant hepatic failure. Clinical investigations include studies of the natural history of chronic type B hepatitis and chronic non-A, non-B hepatitis, evaluations of the efficacy of antiviral agents in the treatment of chronic type B hepatitis, and a controlled trial of immunosuppressive therapy in primary biliary cirrhosis.

Genetics and Biochemistry Branch—
Elizabeth F. Neufeld, Ph.D.

- Biochemical Genetics Section—
  Elizabeth F. Neufeld, Ph.D.
- Molecular Genetics Section—
  R. Daniel Camerini-Otero, M.D., Ph.D.

The branch conducts studies in biochemical and molecular genetics. The range of current projects covers a wide field from the very basic (*e.g.*, mechanisms of genetic recombination and gene conversion in mammalian cells, DNA-mediated gene transfer, biosynthesis and transport of lysosomal proteins, and the biochemical and molecular bases of human genetic disorders) to the more applied (development of new diagnostic tests and carrier detection for a number of genetic diseases, preparation of enzymes for replacement therapy, and the development of new techniques for gene purification and transfer).

Metabolic Diseases Branch—
Gerald D. Aurbach, M.D.,
Stephen J. Marx, M.D., and
Allen M. Spiegel, M.D.

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, parathyroid hormone, and calcitonin. The clinical program involves studies of patients with disorders of mineral metabolism. These include patients with hereditary resistance to parathyroid hormone or to calciferols. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is used for *in vitro* studies on control of hormone secretion.

Phoenix Clinical Research Section—
Clifton Bogardus, M.D.,
Barbara V. Howard, Ph.D.,
Lester B. Salans, M.D.,
and Peter H. Bennett, M.B.

This section is currently involved in studies of diseases particularly prevalent among southwestern American Indians. One of the major areas under investigation is diabetes mellitus in the Pima Indian population. This group has the world's highest reported prevalence of type II (noninsulin dependent) diabetes. The geographical proximity of this unique population to the Phoenix area provides an excellent opportunity for insight into the causes and complications of type II diabetes. A problem closely related to the diabetes in this group is that of obesity. These areas are under intensive scientific investigation in both the 24-bed clinical research unit and the basic science research laboratory which are colocated within the Indian Health Service Referral Hospital, Phoenix, Arizona.

Clinical studies currently in progress include whole-body insulin resistance, nutrition-induced alterations in metabolism, lipid and lipoprotein metabolism, and dietary and exercise therapy in the treatment of diabetic patients. The laboratory research is centered around insulin-mediated glucose metabolism in adipocytes from diabetic and nondiabetic donors, fat cell metabolism, as well as a variety of studies supporting the clinical investigations.

Close collaboration with the Epidemiology and Field Studies Section allows investigation into the prevalence of not only diabetes and obesity, but also cardiovascular disease, gallbladder disease, lipid and lipoprotein abnormalities, and rheumatoid arthritis in the Pima Indians.

Basic Research Laboratories

Laboratory of Biochemical Pharmacology—Herbert Tabor, M.D.,
Simon Black, Ph.D.,
Victor Ginsburg, Ph.D.,
Leonard D. Kohn, M.D.,
Kolomon Laki, Ph.D., and
Reed B. Wickner, M.D.

The work of this laboratory includes a large variety of biochemical, genetic, and molecular biological investigations. Included are studies on polyamine synthesis and action, nucleic acid and protein biosynthesis, tryptophan biosynthesis, and yeast and *Escherichia coli* genetics. Studies are also carried out on developmental biology and genomic structure and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

One section is concerned in particular with the structure, function, and bioenergetics of biological membranes and the mechanism by which various effectors—hormones, toxins, neurotransmitters, interferon, and viruses—transmit their information through these members to the interior of the cell. Another subsection studies diverse aspects of the related hormones insulin and somatomedin, including: structure, biosynthesis, mechanism of action, biological role, and genetic syndromes of hormone resistance.

A third section is concerned with the biology and immunology of the complex carbohydrates of animal cell surfaces.

A fourth section is studying the genetic control of replication of a double-stranded RNA virus of yeast and other problems in the genetics of simple eukaryotes.

Laboratory of Biochemistry and Metabolism—
G. Gilbert Ashwell, M.D.,
William B. Jakoby, Ph.D., and
Yale J. Topper, Ph.D.

The laboratory program is directed toward an understanding of the basic biochemical mechanisms involved in both normal and abnormal biological processes. Within this general framework, independent projects cover a broad range of biochemical investigations.

A brief summary of the major areas under study includes an examination of the hormone-dependent differentiation and development of mammary gland tissue in normal and hypophysectomized rats; a detailed study of growth and development whereby the formation of the primary septum of yeast is used as a molecular model for morphogenesis; studies on the mechanism of receptor-mediated endocytosis and glycoprotein-membrane sorting in eukaryotes; and a study of the cluster of enzymatic activities classified as enzymes of detoxication that function in the conjugation of foreign compounds in mammals and the role of cellular factors involved in the biosynthesis and differentiation of lymphocytes in spleen and thymus. In addition to the above general areas, specific projects of individual investigators include a study of the particulate enzymes involved in carbohydrate metabolism, biochemical abnormalities in human cystinosis, genetic control of bacterial membrane proteins, and thermodynamic and kinetic studies on enzymatic mechanisms.

Laboratory of Bioorganic Chemistry—
John W. Daly, Ph.D., and
Donald M. Jerina, Ph.D.

This laboratory's research mission is to elucidate the mechanism of interaction of pharmacologically active substances with biological systems. Research is designed toward the development of new chemical agents as tools for the study of membrane and cytosol functions of cells. New mechanisms of action or metabolism of such agents are also investigated for their potential use as therapeutics. Development and application of modern techniques of organic chemistry for the synthesis, separation, and spectral investigation of these chemical agents and their interactions with macromolecules are emphasized. The goal is to provide insights into the normal and pathologic function of biological systems and to delineate the metabolic formation, fate, and action of physiologically active agents such as amino acids, biogenic amines, cyclic nucleotides, hormones, neurotransmitters, and steroids. Studies include pharmacologically active agents such as natural products, therapeutic agents, toxins, carcinogens, and mutagens.

Laboratory of Chemical Biology—
Alan N. Schechter, M.D., and
Hiroshi Taniuchi, M.D., Ph.D.

The major research programs in this laboratory are concerned with the study of structure, function, and dynamics of macromolecules, with the relationship of the chemistry of macromolecules to cell function, and with the molecular control of gene expression and differentiation. Dr. Schechter's group is studying human erythroid cells to understand the control of globin gene expression and is also using biophysical methods to study the properties of hemoglobin inside erythrocytes. The program also includes clinical studies of hemoglobin diseases. Dr. Dean's group is studying the developmental biology of the mouse oocyte to ascertain the molecular events which accompany and result from fertilization. Dr. Taniuchi's group concentrates on studies of protein folding, changes in protein conformation and function, interactions of proteins with other molecules, and the evolution of proteins. Dr. Chaiken's group is involved in the study of protein-peptide interactions, with particular emphasis on the neurophysin protein. Dr. Steers' group studies blood platelet antibodies and the mechanism of platelet destruction.

Laboratory of Chemical Physics—
Edwin D. Becker, Ph.D., Elliot Charney, Ph.D., William A. Eaton, M.D., Ph.D., William A. Hagins, M.D., Ph.D., and Ira W. Levin, Ph.D.

Research in this laboratory is characterized by the application of modern physical techniques to the study of a wide range of biological problems. Among the current research interests of the staff are: analysis of the kinetics and mechanism of aggregation of hemoglobin-S, study of the association of mononucleotides and of the conformational behavior of polynucleotides, investigations of the excitation of visual photoreceptors and resultant ionic processes in membranes, analysis of excited electronic states of small molecules in the vapor phase and in molecular beams, development of methods for asymmetric synthesis, study of the structural characteristics of model membrane systems, the structure and dynamic behavior of nucleic acids and nucleoproteins, and the dynamics of ligand binding and structural changes in hemoglobin. Much of the research involves the use of a variety of spectroscopic methods—for example, nuclear and electron magnetic resonance, laser-Raman and resonance Raman spectroscopy, electric-field-induced dichroism, ultraviolet and visible microspectrophotometry, and time-resolved absorption spectroscopy with nanosecond lasers.

Laboratory of Chemistry—
Bernhard Witkop, Ph.D., Sc.D., Louis A. Cohen, Ph.D., Arnold Brossi, Ph.D., Cornelius P. J. Glaudemans, Ph.D., and David F. Johnson, Ph.D.

In the oldest laboratory of the Institute (founded June 20, 1905), chemistry is represented in its broadest context in five independent sections investigating the mechanisms of enzymatic reactions and their simulation, medicinal chemistry, steroid hormones, immunochemistry, novel toxins, metabolism, antiviral agents, interferon, and analysis and instrumentation. Some of the recent achievements concern the role of retinoids in bladder cancer, effects of novel colchicine derivatives on microtubules, affinity labeling of glucocorticoid receptors, separation of addictive from analgesic properties in new synthetic morphine substitutes, characterization of sodium channels in electrogenic membranes by a frog toxin, the acetylcholine receptor, development of fluorinated amino acids and biogenic amines as selective probes and inhibitors of enzymatic and metabolic processes, hypoxic cell sensitizers, cytotoxic agents selective for cancer cells, the interaction between antigens and monoclonal antibodies, recombinant hybrid immunoglobulins and the detailed structure of fungal antigens, and chemistry and biochemistry of interferon induction and interferon-related enzymes.

Laboratory of Cell Biology and Genetics—
Harvey B. Pollard, M.D., Ph.D.
Barrie J. Carter, Ph.D., Loretta Leive, Ph.D., Ned Feder, M.D., and
Joe-Hin Tjio, Ph.D.

The laboratory carries out basic studies and collaborative clinical studies relating to secretion of hormones and transmitters from nerve and endothelial cells. Other work includes analysis of endocytosis and phagocytosis by macrophages and macrophage cell lines, structure of nerve and other cell types by both light and electronmicroscopy, immunology and cytogenetics of autoimmunity, and of the molecular biology of viral genomes.

Laboratory of Molecular Biology—
Martin Gellert, Ph.D., Jun-ichi Tomizawa, Ph.D., Gary Felsenfeld, Ph.D., David R. Davies, Ph.D., Robert Martin, Ph.D., H. Todd Miles, Ph.D., and Terrell Hill, Ph.D.

The work of the laboratory is concerned with understanding biological processes in terms of structure and reaction at the molecular level. Research includes direct investigations of biological processes, such as genetic recombination, DNA replication, and protein synthesis, studies of the mechanism of transformation by SV40 (a virus causing tumors in hamsters), and studies of the mechanism of hemoglobin S gelation, the phenomenon that causes sickling of red blood cells in sickle cell anemia. Other investigations are concerned with the structure and chemical properties of biologically important materials. These include studies of the organization of DNA and proteins in chromatin, investigations of protein structure by X-ray diffraction and of nucleic acid and polynucleotide structure by diffraction and spectroscopic methods, and theoretical studies of the mechanisms of free energy transduction, muscle contraction, membrane properties, and biochemical kinetics.

Laboratory of Cellular and Developmental Biology—
Robert T. Simpson, M.D., Ph.D.,
Martin Rodbell, Ph.D.,
Bernard T. Kaufman, Ph.D., and
Robert O. Scow, M.D.

This laboratory consists of four sections devoted to various biochemical and physiological investigations. The Section on Endocrinology investigates hormonal regulation of enzymes involved in chylomicron uptake and metabolism in adipose and mammary tissues, the influence of hormones on cellular development and metabolism, and the disposition of fat and metabolites in the cell as viewed from ultrastructural studies. The Section on Nutritional Biochemistry investigates the structural and functional aspects of dihydrofolic reductase and other enzymes involved in folic acid metabolism and the intermediary metabolism of lipids, carbohydrates, and amino acids in the small intestine. The Section on Membrane Regulation studies the mechanism of action of hormones on adenylate cyclase and other membrane regulatory processes. The Section on Developmental Biochemistry investigates the structure and function of chromatin and the regulatin of gene function during development.

Laboratory of Physical Biology—
R. J. Podolsky, Ph.D., and J. Buck, Ph.D.

This laboratory carries out a broad range of studies. The mechanism of muscle contraction is studied in intact cells and in simplified preparations, using time-resolved X-ray diffraction in conjunction with mechanochemical techniques. Activation of muscle cells is examined by measuring calcium movement between the myofilaments and the sarcoplasmic reticulum in skinned muscle fibers. Lipid dispersions in water are investigated as models of the structure and physical states of lipids in cell membranes. The actions of ionizing radiation on macromolecules are used to determine the *in vivo* size of the functional units for different biological activities (hormone receptors, enzyme complexes, and regulatory units). Electron microscopy is carried out with a wide variety of preparations, and digital image processing techniques are used to enhance resolution. Other subjects under investigation are enzyme organization in unicellular organisms, metamorphosis in insects, human red cell sickling, and biological rhythms and entrainment.

Mathematical Research Branch—
John Rinzel, Ph.D.

The branch conducts research on the mathematical and theoretical aspects of biological problems and the development of analytical and numerical methodology underlying such an approach. The research programs are designed to provide a formal basis and theoretical apparatus for the rational analysis and quantitative interpretation of biological phenomena. *Research is organized around biological subject-matter areas rather than around subdisciplines of mathematics.* Major research topics include transport and consumption of substrates at the tissue-capillary level, electrotonus in neuronal dendritic systems, excitability and auto-rhythmicity in neuroelectric signaling, bifurcation, and stability studies of nerve conduction and diffusion-reaction systems, nonlinear chemical/biochemical oscillations, analysis of nucleic and amino acid sequences, and mathematical modeling of renal functions.

National Institute of Child Health and Human Development

Mortimer B. Lipsett, M.D.,
Director
Arthur S. Levine, M.D.,
Scientific Director, (Director, Intramural Research)
D. Lynn Loriaux, M.D., Ph.D.,
Clinical Director

The Intramural Research Program is broadly concerned with the biological and neurobiological, medical, and behavioral aspects of normal and abnormal human development. In addition to four major clinical research and training programs in the areas of genetics and endocrinology, a diversity of developmental models are under study in eleven fundamental research laboratories, drawing upon observations in bacteria, *Drosophila,* yeasts, viruses, molluscs, frogs, rodents, and subhuman primates. Disciplines employed in these studies include biochemistry, virology, molecular biology, immunology, pharmacology, genetics, cell and neuronal biology, biophysics and theoretical biology, reproductive physiology and developmental psychology.

Each medical staff fellow will devote time mainly to research in the laboratory under the supervision of a senior preceptor. Each is expected to engage in appropriate course work in the basic and/or medical sciences as well as tutorial seminars, and to take an active part in the journal club, lecture series, and other laboratory exercises.

All appointments as medical staff fellows are for a minimum of 2 years with a third optional year. Most fellows elect to remain for 3 full years and are offered this opportunity. For a limited number of highly qualified fellows, additional years of training are possible.

The Intramural Research Program's eleven branches and laboratories are each under the direction of a branch or laboratory chief. Medical staff fellow positions are usually available in all of these areas. The fellows have an exceptional opportunity to become independent scientists in a field of their interest, and to prepare themselves for a career in academic medicine and research.

Prospective applicants wishing further information should write to Arthur S.

Levine, M.D., Scientific Director, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20205. In writing, please be specific as to your interests and the information you require.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research.

Medical staff fellows will be responsible, under the guidance of investigators on the NICHD staff, for the primary medical care of research patients during the first year of their service. During this time, they will serve in the medical services that are associated with the clinically oriented branches of the Institute and assist in the work of the service with inpatient care, consultation and in the outpatient department. The clinical period offers exposure to rich case material and to highly sophisticated approaches to clinical investigation.

The fellow devotes the subsequent time to laboratory research under direction of a senior preceptor in any one of the eleven Institute laboratories. The choice of laboratory is made during the fellow's first 6 months at NIH. No clinical responsibilities are required during the second or additional years for fellows who have chosen nonclinical laboratories.

The NICHD selects nine medical staff fellows each year who participate in one of the four approved clinical subspecialty training programs sponsored by this Institute: (1) adult endocrinology, (2) pediatric endocrinology, (3) gynecologic endocrinology, and (4) human genetics.

Fellows in adult endocrinology apply to the Developmental Endocrinology Branch and participate in the NIH Joint (inter-institute) Endocrinology Fellowship Program which leads to board certification by the American Board of Internal Medicine in the subspecialty of endocrinology and metabolism (see page 5). Applicants must be board eligible in the specialty of internal medicine prior to the initiation of the fellowship. The first year of the fellowship is primarily clinical. Further years are devoted to a research project which may be carried out in any of the eleven branches or laboratories of the NICHD.

Applicants for the pediatric endocrinology fellowship also apply to the Developmental Endocrinology Branch and must have completed PL-3 level training prior to the initiation of the fellowship. The first year is primarily clinical, with pediatric patient care responsibilities in the three endocrinology units associated with the NIH Joint Endocrinology Fellowship Program. The further years are spent in any one of the branches or laboratories of NICHD. This fellowship is approved by the American Board of Pediatrics and leads to board certification in the subspecialty of pediatric endocrinology.

Applicants for the gynecologic endocrinology fellowship apply to the Developmental Endocrinology Branch and must have completed an accredited residency in obstetrics and gynecology prior to the first fellowship year. The fellowship is a cooperative program utilizing the combined clinical facilities of the NIH, the National Naval Medical Center, and the Walter Reed Army Medical Center. The first year is entirely clinical, 6 months being spent on the combined endocrine services of the NIH, and 6 months in the infertility clinics of the two Service hospitals. The following years of the fellowship are spent in a research program that may be undertaken in any of the branches or laboratories of the NICHD. This program is recognized by the American Board of Obstetrics and Gynecology and leads to certification in the subspecialty of gynecologic endocrinology.

Fellows in human genetics apply to the Human Genetics Branch and participate in the NIH Interinstitute Medical Genetics program (see page 6). The program fulfills all of the requirements proposed by the American Board of

Medical Genetics and leads to board certification in this subspecialty. Candidates may be pediatricians or internists, and occasionally represent other medical specialties such as neurology and obstetrics. As with the other NICHD clinical specialty programs, the first year of the fellowship is primarily clinical, with patient care responsibilities on the research wards, in the NIH Genetics Clinic and the NIH-supervised Prenatal Diagnosis Clinic at George Washington University Hospital. The further years are spent in a research program in any NICHD laboratory or branch of the fellow's choice.

Applications for all four of these programs are considered 1 or 2 years in advance of the proposed starting date. Application forms may be obtained from the NIH Medical Staff Fellowship office, Building 10, Room 2N220A, National Institutes of Health, Bethesda, Maryland 20205.

Appointments in Laboratory Research

A limited number of appointments are available which are designed to give highly qualified physicians an opportunity to do basic research in any area of the Institute under the direct supervision of a senior preceptor. Usually physicians enter the appointment after completing internship and at least 1 year of residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises. Fellows with this appointment work exclusively with the branch or laboratory in which they are accepted, and make this choice at the time of initial application.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Medical staff fellows are expected to take advantage of this academic work. (See page 127).

Medical Staff Fellows in Pharmacology (PRAT)

Several of the NICHD laboratories and branches participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in preclinical or clinical pharmacology. For more information about the PRAT program see page 82.

Clinical Research Branches

Developmental Endocrinology Branch—
D. Lynn Loriaux, M.D., Chief
Gordon B. Cutler, M.D.
Bruce C. Nisula, M.D.
Richard J. Sherins, M.D.

The endocrine concomitants of growth, development, and differentiation are examined in this branch. Specific areas of study include the mechanisms underlying the initiation of puberty, the pathophysiology of the syndromes of precocious and delayed puberty, and the treatment of these disorders, including the use of an LHRH agonist analogue as a treatment for gonadally mediated disorders. The role of sex steroid hormones in long bone growth, and the mechanism through which these effects are exerted, are being examined. The treatment of both short and tall stature with agents such as sex steroids and growth factors is an ongoing study. The physiology and biochemistry of the action of hypothalamic releasing hormones in these conditions is also an area of current research.

The mechanism of action of the steroid hormones is under investigation, including studies of the clinical disorders of masculinization, feminization, and glucocorticoid deficiency or excess. In this regard, patients with polycystic ovarian disease, gynecomastia, polyendocrine deficiency, and Cushing's syndrome play an important role in the clinical program of the branch. Two syndromes of resistance to steroid hormone action, testicular feminization and cortisol resistance, are under intensive study as well.

The glycoprotein hormones, TSH, LH, FSH, and hCG, are the subjects of both clinical and basic research studies. Understanding the physiology of regulation of TSH, LH, and FSH secretion by the pituitary is a major goal in this area. The development of new diagnostic procedures involving the glycoprotein hormones and evaluation of their clinical applications are given substantial investigative effort. Clinical disorders of thyroid function and conditions characterized by abnormal glycoprotein hormone secretion are being studied to elucidate the role of molecular heterogeneity in these situations. With respect to mechanisms of action, the regulation of thyroid function through the TSH receptor-adenylate cyclase system is of particular interest.

Human reproduction is another major area of clinical interest. The hormonal control of gonadal development and the basic physiology of gametogenesis are investigated. Clinical investigations of the full range of male and female gonadal disorders and, especially, infertility, are aimed at understanding pathogenetic mechanisms and developing new therapeutic modalities.

Human Genetics Branch—
Michael A. Zasloff, M.D., Ph.D.

The Human Genetics Branch's interests range from studies on the diagnosis and treatment of genetic and developmental disorders of young people to very basic studies on gene expression utilizing recombinant DNA methodology. The intent of the branch's clinical fellowship program is to provide broad exposure to the field of human genetics, including clinical care, clinical research, and basic studies. The first year is devoted to clinical training, and fellows are exposed to a wide spectrum of human genetic disease by rotating through several medical wards of the NIH, as well as genetics clinics of the Johns Hopkins Hospital, the Children's Hospital National Medical Center, and the George Washington University Hospital. During the following 2 years, the fellow conducts laboratory research under supervision of a senior NICHD staff scientist.

- Section on Cellular Differentiation—
  Janice Chou, Ph.D.

This section conducts research on the mechanisms of gene function and regulation during mammalian development. Major emphasis is on the investigation of biochemical and molecular changes associated with normal and abnormal differentiation processes. Techniques utilized include tissue and organ culture, and recombinant DNA methodology.

- Section on Developmental Genetics—
  Anil Mukherjee, M.D., Ph.D.

This section emphasizes biochemical, cellular, and immunological studies on early mammalian development and differentiation. Major interests include the mechanisms by which the fetus is protected from maternal immunological assault during its intrauterine development. In addition, basic and clinical studies are being conducted to understand the basis of ethanol intolerance in man and the etiology of the fetal alcohol syndrome. Techniques utilized include tissue culture and fetal studies on nonhuman primates.

- Section on Disorders of Carbohydrate Metabolism—
  James B. Sidbury, M.D.

This section focuses on the natural history, diagnosis, treatment and pathophysiology of genetic disorders of carbohydrate metabolism, with a special emphasis on the glycogen storage disorders.

- Section on Biochemical Genetics—
  Michael A. Zasloff, M.D., Ph.D., Acting

A combination of clinical and laboratory-based research is used to identify the biochemical etiology of genetic diseases such as cystinosis, adrenoleukodystrophy, galactosemia, glutathione defects, and glucose-6-phosphate dehydrogenase deficiency. This section has concentrated on understanding the pathophysiology of these defects in order to develop new methods of prenatal and neonatal diagnosis and treatment of the patient, as well as detection of heterozygotes.

- Section on Molecular Biology—
  Michael A. Zasloff, M.D., Ph.D.

This section studies basic mechanisms of eukaryotic gene expression as a means of understanding disease processes. Current studies include genomic organization and expression of human tRNA genes, the mechanism of nuclear RNA transport, the molecular mechanism of thyroid hormone action, and the isolation of the gene for neuronal enolase. Techniques utilized include recombinant DNA methodology, amphibian oocyte injection, and DNA transfer into somatic cells. Clinical interest include the pathophysiology and natural history of fibrodysplasia ossificans progressiva, a heritable disorder of connective tissues characterized by uncontrolled heterotopic ossification. Several new treatment protocols utilizing novel synthetic retinoic acids are currently under study.

Child and Family Research Branch—
Frank A. Pedersen, Ph.D., Acting

Research in this branch has concentrated on behavioral investigations of infants, young children, and their families. One group of studies is concerned with early family relationships—the transition to parenthood as well as mother-infant and father-infant interaction. Factors that affect the infant's experiences in the home environment are being traced, including events surrounding childbirth (e.g., Caesarean or vaginal delivery), the infant's separation experiences, and maternal employment. A second group of studies has focused on early cognitive and motivational development. New methods have been developed to assess the longitudinal course of mastery motivation. We are investigating its origins in the home environment and the relationship of mastery motivation to intellectual development. A third area of research concerns children with endocrine disorders of growth and development. Observational and self-report procedures are used to study the psychological consequences of these disorders and how children and their families cope with the stress produced by such a condition. Medical staff fellows work with a senior investigator and receive training in a range of behavioral research methodologies.

Basic Research Laboratories

Office of the Scientific Director—

- Section on Growth Factors—
  Gordon Guroff, Ph.D.

This section is studying the mechanism of action of enzymes of neurochemical interest, the biosynthesis and degradation of macromolecules in neural tissue, and the mechanism of action of nerve growth factor. Other studies concern the evaluation of the effects of excesses or deficiencies of intermediary metabolites on cellular differentiation.

- Section on Viruses and Cellular Differentiation—
  Arthur S. Levine, M.D.

Viruses which influence differentiation are used to probe the developmental program of macromolecules that regulate changes in the phenotypes of normal and transformed animal cells. The host's immune response to these modified phenotypes is also under study. The techniques of virology, tissue culture, cell hybridization, molecular biology, and immunology are employed.

- Laboratory of Developmental Neurobiology—
  Phillip G. Nelson, M.D., Ph.D.

The neurobiologic mechanisms relevant to development of the nervous system are investigated with emphasis on studies at the cellular membrane and molecular levels. The basis for short- and long-term interaction between nerve cells is studied electrophysiologically and biochemically. The central neural mechanism underlying sensory discrimination in primates is studied by electrophysiologic and behavioral techniques. Combined molecular and behavioral methods are used in the analysis of experiential modifications of brain function.

- Section on Brain and Behavior—
  David Symmes, Ph.D.

Electrophysiologic correlates of sensory coding and discriminative behavior are analyzed with microelectrode computer techniques. The focus of interest is on vocal communication among subhuman primates and its possible relationships to human speech.

- Section on Neurobiology—
  Phillip G. Nelson, Ph.D.

Tissue-cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied, using intra-cellular electrophysiologic techniques and correlative light and electron microscopic morphologic methods. Neuron-specific biochemical assays are used to analyze mechanisms of neurodifferentiation. Long-term interactions between nerve and muscle, and the influence of electrical activity on neural development, are of particular interest. Molecular genetic techniques are being used to study nervous system development.

- Section on Neuroendocrinology—
  David C. Klein, Ph.D.

Research activities involve environmental, pharmacologic, developmental, and biochemical factors critical to the metabolism and function of the pineal gland. Current studies on this model of neural and neuroendocrine regulation focus on the molecular mechanism involved in the transsynaptic adrenergic cAMP regulation of gene expression. In addition, control of reproductive physiology by the pineal gland is investigated.

Laboratory of Neurochemistry and Neuroimmunology—
Harold Gainer, Ph.D.

This laboratory utilizes the tools of molecular biology and immunology in a cell biological context to study the biosynthesis, packaging, transport, and secretion of biologically active peptides and proteins in neuronal systems. Various model neuronal systems in organisms ranging from molluscs (squid) to vertebrates (e.g., frog, chick, and rat) are used to examine the development and function of defined neural pathways *in vivo*. Organotypic cultures of these systems are also studied. Techniques which are used include peptide chemistry, monoclonal antibodies and immunochemistry, light and electron microscopy, immunohistochemistry and cytochemistry, subcellular fractionation, and tissue culture.

- Section on Functional Neurochemistry—
  Harold Gainer, Ph.D.

This section focuses on the development and functional organization of peptidergic neurons in the hypothalamus. This includes consideration of the extracellular mechanisms involved in the regulation of specific peptide biosynthesis, secretory vesicle interactions with cytoskeletal proteins during axonal transport, and with membrane associated proteins during secretion. Characterizations of specific proteins within these neurons by correlative ultrastructural and immunochemical techniques are made, and the functional roles of these proteins are investigated in both developing and mature neurons. The roles of proteases and membrane proteins involved in neuron:neuron and neuron:glia interactions during development and regeneration are studied.

- Section on Cellular Neurobiology—
  Y. Peng Loh, Ph.D.

This section is concerned with post-translational modifications of proteins and peptides (e.g., limited proteolysis, acetylation, amidation, etc.) in endocrine cells and neurons. Molecular maturation mechanisms are correlated with their intracellular (organelle) locations, and the molecular signals and mechanisms which determine the intracellular routing of specific proteins and peptides are investigated. The effects of intercellular messengers (e.g., neurotransmitters) on the regulation of specific protein and peptide expression are studied. Recombinant DNA techniques are employed to characterize the genes responsible for specific post-translational processing enzymes.

Laboratory of Molecular Genetics—
Igor Dawid, Ph.D.

Investigators in this laboratory use the tools of molecular and cellular biology to answer questions about gene transmission and recombination, and the regulation of genetic functions during development. The range of model systems under investigation includes bacterial and animal viruses, tumor cells, immune cells, *Xenopus* embryos and the fruit fly *Drosophila melanogaster*. Recombinant DNA technology and gene transfer methods are emphasized.

- Section on Developmental Biology—
  Igor Dawid, Ph.D.

Interest is focused on the molecular genetics of development. Gene expression during early embryonic stages of *Xenopus* is studied with the aid of cDNA libraries. Developmental mutants and transposable DNA elements are investigated in *Drosophila*, using both classical and molecular genetics. Cultures of functional regulatory and effector T-cells are established and characterized in order to map pathways of cell circuitry within immune systems. Certain aspects of retrovirus biology are investigated with a focus on RNA-dependent DNA polymerase. The development of novel vectors is pursued for the introduction and expression of isolated genes in animal cells.

- Section on Molecular Regulation—
  Michael Cashel, M.D., Ph.D.

The structure and regulation of activity of genes for ribosomal RNA in *E. coli* are studied using techniques that include *in vitro* mutagenesis. Determinants for RNA processing and enzymes involved in this process are studied in bacteria and in animals.

- Section on Molecular Structure—
  Jacob Maizel, Ph.D.

Experiments are directed towards a study of the biology of several animal viruses, including adeno-, rhino- and poliovirus. Interest is focused on computer-assisted analysis of nucleic acid sequence and secondary structure.

- Section on Microbial Genetics—
  Robert Weisberg, Ph.D.

Mechanisms of genetic recombination are studied in bacteriophage lambda. Experiments proceed at the level of genetics, nucleic acid structure, and enzymatic reactions.

- Section on Animal Viruses—
  Heiner Westphal, M.D.

DNA-mediated gene transfer into mouse embryos is carried out with the aim of studying the regulation of expression of introduced genes in the intact animal. Transcriptional regulation of adenovirus is studied by several techniques including DNA and RNA injection into cultured cells.

Developmental Pharmacology Branch—
Daniel W. Nebert, M.D.

Research in this branch has concentrated on attempts to understand gene expression at the molecular level. This branch studies mechanisms of hormone action, enzyme regulation with particular reference to the induction of drug-metabolizing enzymes by drugs and other environmental chemicals, teratogenesis, neonatal "imprinting," and the cellular uptake of amino acids and other small molecules across membranes. Other projects employ the methods of clinical pharmacology and pharmacokinetics. Goals include the development of clinical tests designed to improve diagnosis and therapy of human diseases ranging from glucocorticoid hormone resistance to inborn errors of metabolism. Clinical tests are also being designed for predicting increased risk of drug-induced birth defects and chemically-induced malignancies.

- Section on Pharmacogenetics and
  Molecular Teratology—
  Daniel W. Nebert, M.D.

Inbred strains of mice and cells in culture are combined with recombinant DNA and ancillary techniques to study the regulation and gene expression of drug-metabolizing enzymes. Related research projects are in the areas of teratology, neonatal imprinting, control of endogenous drug-metabolizing enzymes by hormones, growth factors, and clinical pharmacology.

- Section on Regulation of Gene Expression—
  Howard J. Eisen, M.D.

This section examines the molecular mechanisms by which steroid hormones, drugs, and environmental contaminants alter gene expression in target cells. Emphasis is on (a) the use of genetic models of hormone- or drug-resistance to study the biochemical functions of receptor proteins and (b) the development of methods for isolation and immunochemical characterization of receptors.

- Section on Drug Biotransformation—
  Ida S. Owens, Ph.D.

Investigations are directed toward "Phase II" drug metabolism, i.e., conjugation reactions in which enzymes (UDP glucuronosyltransferases) use as substrates bilirubin, endogenous steroids, or oxygenated drugs, carcinogens and other environmental pollutants. Mechanisms of gene expression and enzyme induction are explored via the use of immunochemical and recombinant DNA techniques, inbred strains of mice, and normal and mutant cells in culture. An additional goal is to understand the basis for human genetic diseases involving variants of the Phase II enzymes.

Laboratory of Developmental and Molecular Immunity—
John Robbins, M.D.

The laboratory conducts research into the developmental and molecular biology of "natural," genetic, and immunization-induced immunity to bacterial and other antigens. Emphasis has been placed on the study of pathogenic mechanisms, antigenic molecules, and their purification and characterization, and on the protective mechanisms of the host. The hybridoma and recombinant DNA technologies, as well as the methods of macromolecule purification, have been applied to these problems.

- Section on Bacterial Disease Pathogenesis and Immunity—
  John Robbins, M.D.

A primary objective of this group has been to devise methods to increase the immunogenicity of the capsular polysaccharides of *H. influenzae* type b, pneumococci, and *E. coli* associated with invasive human diseases. Semisynthetic conjugates of these polysaccharides have been prepared which increase their immunogenicity and convert their immunogenic properties to those of T-cell dependence. These conjugates are also used to characterize the ontogeny and genetic control of the serum antibody response in humans.

In another area of research, the physical-chemical characteristics of the pertussis toxin (i.e., the subunit structure), and their relation to this molecule's toxic and protective activities, are being studied. Monoclonal antibodies to the subunits of the toxin will be used as probes for the cloning of the gene(s) involved in its synthesis.

The effects upon the mammalian lymphoid system and the gastrointestinal tract induced by bacterial products are also being investigated. The phenomenon of runting, as an immunopathological event, is being studied using highly purified bacterial components that are reactive with gastrointestinal cells.

- Section on Immunoregulation and Cellular Control—
  Edgar Hanna, Ph.D.

Interest is focused on cellular, molecular, and genetic mechanisms involved in regulation of immune systems. Monoclonal and functional regulatory and effector T-cells are established as cloned lines. They are phenotyped in order to map pathways of cell circuitry within immune systems.

- Section on Molecular Genetics of Immunity—
  Keiko Ozato, Ph.D.

Modification of transplantation antigen genes at the DNA level is studied in order to determine the structural basis for immunological polymorphism and the function of the gene products. Hybrid or mutant mouse H-2 genes are employed in the examination of serological polymorphism and T-cell recognition. Activation of paternal transplantation antigen genes is studied in developing embryos. The phenomenon of immunological unresponsiveness in pregnant females is explored at the level of molecular mechanisms. Monoclonal antibodies for detecting complex antigens in neuronal and neuroendocrine tissue are developed and studied.

- Section on Macromolecular Analysis—
  Andreas Chrambach, Ph.D.

This section specializes in the development of gel electrophoretic methods, both analytical and preparative, and in the application of these methods to the separation and isolation of native macromolecules, especially those relating to immunity.

Laboratory of Theoretical and Physical Biology—
David Rodbard, M.D.

This laboratory studies the metabolism of calcium, phosphorous, steroids, carbohydrates, and amino acids, in clinical studies and in single cells. Mechanisms of drug and hormone receptor interactions and antigen-antibody reactions are under investigation. We utilize several biophysical methods, including mass spectrometry and nuclear magnetic resonance, combined with mathematical, statistical, and computer-based methodology. Fellows will be trained in the relevant methods, in accordance with their interests and objectives.

- Section on Metabolic Analysis—
  Alfred L. Yergey, Ph.D.

Clinical endocrine and metabolic studies are performed to investigate the kinetics of metabolism of steroids, carbohydrates, amino acids, calcium, and other metals in humans during development, pregnancy, and in various disease states. Stable (nonradioactive) isotopic tracers are used since they represent completely benign probes into the systems of interest. The time course of serum concentrations of the isotopes is measured by mass spectrometry. Computerized mathematical modeling, optimization of experimental design, and statistical analyses are used to characterize the physiology and pharmacokinetics of these multicompartmental systems.

- Section on Molecular Pharmacology—
  Jack S. Cohen, Ph.D.

Molecular interactions of pharmacologic interest are studied by nuclear magnetic resonance (NMR) spectrometry in solution. Studies include conformational variance in DNA as a result of solution conditions and base sequence, and their effects upon drug and protein binding. Noninvasive NMR studies of cell metabolism are carried out with cells grown in culture embedded in a gel matrix. These investigations enable us to detect alterations in metabolism as a result of disease state or treatment.

- Section on Theoretical Biology—
  David Rodbard, M.D.

Combined theoretical and experimental studies are used to examine mechanisms of complex receptor systems for drugs, hormones, and neurotransmitters (e.g., enkephalins). The section is concerned with optimization, validation, and data processing for radioimmunoassays and related immunological methods, and mechanisms of antigen-antibody reactions. The section is also concerned with the development of new applications of computers in clinical medicine.

Pregnancy Research Branch—
Gary D. Hodgen, Ph.D.

The interests of this branch range from the physiology of pregnancy (including the identification of genetic and developmental factors which contribute to perinatal, fetal, and maternal morbidity and mortality) through fertility regulation and toxicologic aspects of ovarian function, to fertilization and implantation. Particular emphasis is given to diagnostic and therapeutic considerations in female infertility, including: ovulation induction, endometriosis, tubal physiology, and pelvic adhesions. These studies employ a variety of animal models, as well as laboratory aspects of clinical investigation. Fellows in gynecologic endocrinology, who apply through the Developmental Endocrinology Branch (and serve in the clinical programs at NIH, Walter Reed Army Hospital, and the National Naval Medical Center during the first year) may spend the next 1 or 2 years in laboratory investigation in collaboration with a senior investigator in this branch.

- Section on Endocrinology—
  Gary D. Hodgen, Ph.D.

Basic research is conducted in reproductive endocrinology and in laboratory aspects of clinical investigation. Major emphasis is placed on nonhuman primates for studies of ovarian function and pregnancy, and on antenatal diagnosis linked to fetal therapy, including medical and surgical interventions.

Endocrinology and Reproduction Research Branch—
Kevin J. Catt, M.D., Ph.D.

Current research is focused on the mechanisms controlling hormone secretion and action, with particular reference to hypothalamic-pituitary hormones and their receptor-mediated responses in endocrine target cells. Studies in progress include the analysis of receptors and actions of hypothalamic peptides (GnRH, somatostatin, CRF, GRF), angiotensin II, ACTH, prolactin, and gonadotropins. The characterization and isolation of peptide hormone receptors, clarification of plasma-membrane related second messenger systems, and the elucidation of the control of steroidogenesis and glycogenolysis, are major goals of the branch research program.

- Section on Hormonal Regulation—
  Kevin J. Catt, M.D., Ph.D.

Receptor-mediated aspects of peptide hormone action are studied in target tissues regulated by hypothalamic peptides, angiotensin II, and gonadotropins. The mechanisms of peptide hormone action are investigated in isolated pituitary cells (GnRH, CRF, GRF, somatostatin, angiotensin II), adrenal cells (ACTH, angiotensin II), and steroidogenic cells of the testis and ovary (LH, FSH, prolactin, GnRH). In these target cells, the roles of cyclic nucleotides, calcium-dependent processes, and phospholipid turnover, are studied in relation to the control of cellular activity by the regulatory hormones.

- Section on Molecular Endocrinology—
  Maria Dufau, M.D., Ph.D.

This group investigates the molecular basis of peptide hormone action, with particular emphasis on the control of gonadal function; analyzes the nature of gonadotropin receptors and activation of steroid biosynthesis in testis and ovary; and investigates the properties and biological activity of circulating gonadotropins in physiologic regulation and clinical disorders of pituitary and gonadal function.

National Institute of Dental Research

Harold Löe, D.D.S., Dr. odont.
Director
Marie U. Nylen, D.D.S.,
Dr. Odont., h.c.,
Director, Intramural Research
Bruce J. Baum, D.M.D., Ph.D.,
Clinical Director

The National Institute of Dental Research recruits about two or three dental and one or two medical staff fellows each year. Initial assignments are for 2 years and may be extended for a third year. Appointments usually begin on July 1. Selection of candidates is based on program needs and qualifications of candidate. The chiefs of branches and sections screen applications, carry out personal interviews of candidates, and make recommendations to the clinical director, who will make final selection. Selection of candidates for research positions will be made following personal interviews by chiefs of laboratories and branches who have vacancies occurring within their programs. After results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical and basic research program areas and the names of the program chiefs are listed below. A brief sketch of the clinical research areas is provided. Prospective applicants desiring more information should write to Marie U. Nylen, D.D.S., Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, MD 20205.

Dental Staff Fellows

Dental staff fellows spend much of their first year (about two-thirds) providing a wide range of care for patients at the Clinical Center. The remaining time is spent in clinical or laboratory research. The second (and third) year will be spent primarily (about 80 percent) engaged in supervised research with some clinical care responsibilities. Dental staff fellows must have a dental licensure in the United States, a minimum of 1 year hospital dental experience, and a desire for a career in academic dentistry.

Medical Staff Fellows

The medical staff fellow is assigned to one of the clinical research programs within which he or she carries out both clinical and laboratory studies. In addition, the medical staff fellow is responsible for performing medical evaluation and followup of patients accepted under one of the Institute's research protocols. Medical staff fellows may also be assigned to one of the basic research laboratories where they devote all their time to participating in laboratory research. One year of internship and at least 1 year of residency should be completed before the appointment begins.

Clinical Research Branches

Diagnostic Systems Branch—
Richard L. Webber, D.D.S., Ph.D.

Investigations are directed toward research and development of diagnostic techniques. Specific emphasis is placed on radiologic and other noninvasive analysis techniques. The main focus is on interdisciplinary investigations linking clinical expertise with technical competence to facilitate a systems approach to diagnostic problems. Diagnostic systems are designed, modeled, and evaluated with the use of digital simulation techniques. Prototype systems are then developed and tested clinically. Bases for improvement include matching of system elements, image enhancement, and new geometric bases for quantitative analysis of tissue morphology.

Neurobiology and Anesthesiology Branch—
Ronald Dubner, D.D.S., Ph.D.

- Neural Mechanisms Section—
  Ronald Dubner, D.D.S., Ph.D.

Research on peripheral and central nervous system mechanisms of oral-facial sensation is performed by this laboratory. In one major study, behavioral responses in monkeys trained in pain and temperature discrimination tasks are correlated with single-cell neuronal activity recorded at various levels of the trigeminal system. Other research involves combined neurophysiologic and anatomical studies of the organization of the spinal cord dorsal horn using the intracellular horseradish peroxidase method and light and electron microscope analysis of structural correlates of neural function.

- Neurocytology and Experimental Anatomy Section—
  Stephen Gobel, D.D.S.

This section uses a variety of anatomical approaches to study how noxious inputs, which are transmitted by primary trigeminal neurons, are processed in the central nervous system. Major efforts are directed at the study of the morphology, synaptic connections, and development of second-order interneurons and projection neurons in the medullary (trigeminal nucleus caudalis) and spinal dorsal horns, as well as the identification of the major sources of brainstem descending inputs to these neurons. In addition, a series of experiments are being conducted in which the effects of peripheral nerve transection on synaptic connections are studied.

- Clinical Pain Section—
  Ronald Dubner, D.D.S., Ph.D.

This group conducts research on the assessment of acute and chronic pain and the evaluation of new pain control methods. In psychophysical studies, verbal descriptor scales and metric analog scales are used to measure experimental and clinical pain responses in normal subjects and chronic pain patients. These scales also are employed to assess post-surgical pain and the effects of endogenous pain-suppressing mechanisms. Other studies include the development and application of sedative agents and techniques used in the control of anxiety and apprehension in patients. Research includes physiologic, pharmacologic, and psychological studies of the efficacy and toxicity of combinations of intravenous sedative drugs used in extensive ambulatory surgical procedures.

National Caries Program: Caries Prevention and Research Branch—
Ralph A. Frew, D.D.S., M.P.H.

- Biometry Section—
  Janet Brunelle, M.S.
- Community Programs Section—
  Herschel Horowitz, D.D.S., M.P.H.
- Preventive Methods Development Section—
  Horace M. Stiles, D.D.S., M.P.H., Ph.D.
- Etiology Section—
  Michael F. Cole, B.D.S., Ph.D., Acting

This branch investigates the etiology, pathogenesis, and methods for the prevention of dental caries. Attention is paid to the factors that influence formation of dental plaque. The interaction of dietary constituents with the microbial flora of the mouth is studied. Emphasis is also placed on the natural defense mechanisms in the mouth by lactoferrin, lactoperoxidase, and antibodies as they relate to dental caries. Methods to enhance effectiveness of fluorides are explored. Epidemiologic studies of communities with unusual prevalence of caries are carried out. Clinical trials of caries preventive agents and research into improved methods of analyzing data are conducted.

Clinical Investigation and Patient Care Branch—
Bruce J. Baum, D.M.D., Ph.D.

- Clinical Investigations Section—
  Bruce J. Baum, D.M.D., Ph.D.
- Patient Care Section—
  Michael W. Roberts, D.D.S., M.S.D.

This branch conducts laboratory and clinical studies on normal cellular regulatory mechanisms and alterations occurring in oral disease states. Particular emphasis is placed on exocrine secretion, bone formation and resorption, and white cell functions. Exocrine studies in salivary glands involve hormone/neurotransmitter-receptor interactions, signal transduction events (cyclic nucleotides, Ca^{++}, phospholipids), protein processing and translocation, and water and electrolyte secretion. Mineralization studies involve the isolation and characterization of factors that promote osteogenesis and the regulation, by various hormones, of osteoblasts. White cells are studied particularly as involved in periodontal diseases. Cell types studied include neutrophils, lymphocytes, and macrophages. Investigations focus on the regulation of one white cell type by another, the role of reactive oxygen species in immune responses, and probing the mechanism of activity of specific periodontopathic organisms utilizing monoclonal antibodies.

Basic Research Laboratories

Laboratory of Oral Biology and Physiology—
Arthur R. Hand, D.D.S.

- Experimental Morphology Section—
  Arthur R. Hand, D.D.S.
- Enzyme Chemistry Section—
  John E. Folk, Ph.D.

The laboratory conducts basic research

on the structure and function of oral tissues, and on the posttranslational modification of proteins. Major emphasis is placed on elucidation of basic mechanisms of cellular secretion. Topics of current studies in this area include the role of the Golgi apparatus in protein transport and packaging; endocytic mechanisms, lysosomal function, and membrane dynamics; structure and function of intercellular junctions; cellular mechanisms regulating gene expression, protein synthesis, and exocytosis; and cell surface receptor localization in salivary glands. Studies of proteins and enzymes are aimed at elucidating their mechanisms of action and biological significance. Particular emphasis is placed on transglutaminases, enzymes which catalyze covalent crosslink formation, and a eukaryotic initiation factor which contains an unusual amino acid formed posttranslationally.

Mineralized Tissue Research Branch—
Arthur R. Hand, D.D.S., Acting

- Bone Cell Biology Section—
  A. H. Reddi, Ph.D.
- Proteoglycan Chemistry Section—
  Vincent C. Hascall, Ph.D.
- Skeletal Biophysics Section—
  Edward D. Eanes, Ph.D.
- Skeletal Matrix Biochemistry Section—
  John D. Termine, Ph.D.

The branch conducts basic research on the physiology, biochemistry, and physical chemistry of skeletal development, regulation, and disorders. Major emphasis is placed on the characterization of mineralized tissue macromolecules including collagens, proteoglycans, and tissue-specific noncollagenous matrix proteins; identification of mechanisms involved in tooth, bone, and cartilage formation; physical and chemical characterization of mineral-forming systems and mineral structure; characterization of the macromolecular organization of skeletal tissue matrices by biophysical techniques; and characterization of the molecular pathology of skeletal tissue diseases. Investigators in the branch use a wide variety of *in vivo*, *in vitro*, and synthetic model systems to explore areas such as the role of bone matrix-derived factors in differentiation of cartilage and bone; macromolecular relationships and matrix-mineral interactions in bone, dentin, and enamel; structure of cartilage proteoglycans and regulation of their biosynthesis and degradation; and ionophore-mediated calcium transport and apatite formation.

Laboratory of Developmental Biology and Anomalies—
George R. Martin, Ph.D.

- Connective Tissue Section—
  George R. Martin, Ph.D.

Research is directed toward the elucidation of teratogen-induced and inherited malformations. Projects include studying molecular mechanisms of cellular development, migration, and tissue formation and interaction. Drugs are used to probe these steps. Alterations in the production of such macromolecules as glycoproteins, collagen, and proteoglycans are also studied. Studies are under way on the regulation of gene activity using recombinant DNA technology. Our emphasis is on normal, mutant, fetal, and malignant cells from bone, cartilage, and other connective tissues. Medical staff fellows in this laboratory are encouraged to pioneer new research areas.

Laboratory of Microbiology and Immunology—
Stephen E. Mergenhagen, Ph.D.

- Microbiology Section—
  Charles L. Wittenberger, Ph.D.
- Cellular Immunology Section—
  Joost J. Oppenheim, M.D.
- Humoral Immunity Section—
  Ann L. Sandberg, Ph.D.
- Clinical Immunology Section—
  Reuben P. Siraganian, M.D., Ph.D.

Research in microbiology focuses on bacterial ecology and pathogenesis, regulatory mechanisms in the metabolism of carbohydrates by oral bacteria, and on bacterial genetics, with emphasis on plasmid biology. The immunology programs consists of studies on the purification and properties of lymphokines and monokines which are involved in the induction of immunity and inflammation, the regulation of connective tissue metabolism by lymphocytes and macrophages, and the biochemistry of immediate hypersensitivity reactions. While a dental or medical staff fellow is assigned to one of the sections and will work under a senior investigator, considerable opportunity exists for collaboration with scientists in other components of the laboratory.

Laboratory of Oral Medicine—
Abner Louis Notkins, M.D.

The laboratory conducts clinical research on diseases of the oral cavity. The interdisciplinary program emphasizes virology, oncology, and endocrinology. Present research projects focus on the molecular basis for recurrent and persistent viral infections (e.g., herpes simplex), with emphasis on recombinant DNA technology; the etiology and pathogenesis of leukoplakia and papillomas of the oral cavity; virus-induced immunopathology; the application of monoclonal antibody techniques to isolate viral variants; the influence of viral receptors in determining susceptibility to infection; the role of interferon in autoimmune diseases; the etiology of various dermatologic disorders including apthous ulcers; the role of viruses and immunologic factors in diseases of the exocrine glands (e.g., Sjögren's syndrome and salivary gland tumors) and endocrine glands (e.g., diabetes mellitus); and double-blind clinical trials to evaluate the effectiveness of various drugs in the treatment of oral lesions.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D.,
Director

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biologic factors in the environment that can adversely affect man, to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents, and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods, the interaction of multiple agents resulting in enhanced effects, and the modifying effects of variable physical and biologic states within man on the susceptibility to and course of disease induced by these agents.

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, North Carolina. NIEHS is the only one of the 11 Institutes comprising the National Institutes of Health located away from the campus in Bethesda, Maryland.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University of Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, seminars, and other scientific and professional activities associated with the universities.

Medical Staff Fellows

Medical staff fellows work at NIEHS under the direction of Dr. David Rall, Director, and a laboratory or branch chief in the Institute. Each fellow will work directly under a senior scientist in an area of research chosen by the fellow and the Institute. The initial appointment is for 2 years. These appointments are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. NIEHS does not have clinical facilities; however, medical staff fellows may work out informal arrangements with the clinical staff at the University of North Carolina and/or Duke University Medical School. Prospective applicants desiring more information should write to the Scientific Director, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

Intramural Research Laboratories

Laboratory of Pharmacology—
James R. Fouts, Ph.D.

The toxic effects of low-level and/or chronic exposure to environmental constituents or contaminants on mammals and marine species are studied in this laboratory. Interactions (on or within the animal) of these environmental factors with each other and with drugs are also studied. Projects currently under way include: toxication-detoxication systems in the liver, lung, and skin and effects of pollutants on these systems and the balance between toxication and detoxication reactions; age-related changes in toxication-detoxication systems in various organs; uptake, storage, metabolism, and release of chemicals in the lung and liver; species differences in xenobiotic disposition and metabolism; and studies on the formation and metabolism of reactive metabolites of hydrocarbons in various marine species and purification and comparison of components of toxication-detoxication systems in various organs.

Laboratory of Reproductive and Developmental Toxicology—
Robert L. Dixon, Ph.D.

Scientific efforts are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis with *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratology potential; study the molecular mechanisms underlying cellular differentiation; evaluate perinatal aspects of enzymology, endocrinology, and pharmacokinetics with regard to environmental toxicity; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects that do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of toxicity with the use of *in vitro* cells and tissues, lower animals, and biochemical test systems.

Laboratory of Behavioral and Neurological Toxicology—
Clifford L. Mitchell, Ph.D.

Research is concerned with the study of changes in behavior and neurologic function produced by long-term exposure to low levels of many chemical and physical agents present in the environment. Special consideration is being given to the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurologic abnormalities, studies concerning the mechanisms whereby environmental factors produce behavioral and neurotoxic effects, and studies concerning the conditions that predispose individuals to the behavioral and neurotoxic effects of environmental factors.

Laboratory of Pulmonary Function and Toxicology—
Paul Nettesheim, M.D.

The long-range objectives of this laboratory are to obtain through animal studies information needed to provide the scientific basis for the prevention of respiratory diseases which might have an environmental etiology. The intramural program is studying mechanisms of pulmonary biology and pathology in appropriate experimental models. Research is being pursued in pulmonary endocrinology, prostaglandins, biochemical pathology, environmental carcinogenesis, pulmonary cell biology, and pulmonary pathology.

Laboratory of Environmental Biophysics—
Colin F. Chignell, Ph.D.

This laboratory is involved in several studies on the biologic effects of physical factors in man's environment. At present, the programs concentrate on biologic effects of microwave radiation and noise, singly and in combination with other factors. The effects of microwaves on reproduction and nerve functions (isolated nerves and activities of the central nervous system as reflected in behavior) are under study. Noise effects on various inner ear functions are being studied in combination with ototoxic drugs and heavy metals. New methods have been developed for quantifying microwave doses and for studying sound effects on inner ear physiology and biochemistry. Sophisticated spectroscopic techniques are used to study the molecular interaction of environmental agents with biologic systems.

Laboratory of Environmental Chemistry—
James D. McKinney, Ph.D.

This branch supports research programs and collaborates with Institute laboratories on studies on the chemistry of suspect environmental agents. The branch utilizes, develops, and improves analytical methodology for specified agents which includes immunoassay and instrumental methods such as mass and magnetic resonance spectrometric techniques and high-pressure liquid chromatography. Suspect environmental agents and their conversion products are synthesized and characterized. Research studies on environmental agents, biological materials, and their metabolites emphasize biomechanism elucidation.

Laboratory of Animal Genetics—
Burke Judd, Ph.D.

This laboratory concentrates on studies on the genetic structure of populations and on the structural and functional organization of higher eukaryotic genes, using model systems such as *Drosophila* and cultured mammalian cells. A group in genetic enzymology seeks to develop rapid and efficient methods for the purification of specific macromolecules, proteins, and nucleic acids. One project in chemical genetics focuses on the analysis of mutant mammalian proteins and DNA using primary sequence analysis.

Laboratory of Molecular Genetics—
John W. Drake, Ph.D.

Research in this laboratory is concerned with the chemical nature of the mutation process, especially the nature of the initial damage to or spontaneous alteration of DNA and its subsequent enzymatic processing. Genetic and biochemical analyses are used with both prokaryotic systems and model eukaryotic systems such as yeasts and cultured mammalian cells. The laboratory also provides general services for other laboratories, such as prokaryotic chromosome mechanics, including recombinant DNA and strain synthesis. Studies aimed at developing or improving microbial screening systems for detection of chemical mutagens are also pursued.

Laboratory of Biochemical Genetics—
Heinrich V. Malling, Ph.D.

This laboratory is concerned with studying mechanisms for induction of mutations in mammalian cells *in vivo* and *in vitro*; development and validation of test systems for detecting mutations in both mammalian somatic and germinal cells; correlating mutation induction with physiologic and biochemical endpoints; and, ultimately, facilitating evaluation of risks of exposure of human populations to environmental mutagens. Research is done on characterizing markers for mutation, such as monospecific fluorescent antibodies for mutant hemoglobin and mutant enzymes in sperm, and refining and validating automated systems, such as the cell sorter, for monitoring mutations in larger numbers of samples.

Biometry and Risk Assessment Program—
David G. Hoel, Ph.D.

The Biometry and Risk Assessment Program conducts basic and applied environmental health-oriented research in the areas of risk assessment, statistics, biomathematics, and epidemiology. In addition it assumes responsibility for data management and statistical analysis in the Toxicology Research and Testing Program, and provides statistical, mathematical, data processing, and computer engineering support to the other programs of the Institute. Organizationally, the program is divided into a Statistics and Biomathematics Branch, an Epidemiology Branch, and a Computer Technology Branch.

Statistics and Biomathematics Branch—

The Statistics and Biomathematics Branch conducts a broad research effort ranging from statistical analysis to biomathematical modeling aimed at developing new or improved methods for quantitative risk estimation, particularly in the areas of carcinogenesis, mutagenesis, and reproduction. Branch scientists also maintain an active research program in statistical methodology relevant to design and analysis issues arising in laboratory experimentation with special emphasis on toxicological screening assays.

Epidemiology Branch—

The Epidemiology Branch initiates field studies of human disease, particularly chronic disease, due to environmental pollutants. The branch also investigates the effects of environmental toxins on fetal and child development and conducts basic and applied research in laboratory support methodology involved in the monitoring of human populations.

Computer Technology Branch—
Thomas A. Clemmer, M.S.

The Computer Technology Branch operates the Institute's computer systems and provides programming consultation services, including software systems development, to Institute personnel. It also maintains an active computer engineering group and furnishes systems analysis and project management support to various groups throughout the Institute.

Toxicology Research and Testing Program—
John A. Moore, D.V.M.

The Toxicology Research and Testing Program—the NIH operating component of the National Toxicology Program—develops, validates, and evaluates methods for toxicity testing of chemicals and other environmental agents; is responsible for toxicity testing, using both short- and long-term bioassays, to determine or ascertain toxicity of chemicals and other environmental agents; coordinates and communicates test development and testing program with other government agencies; and disseminates results of research, testing, methods development, and validation efforts to the scientific and public communities and to the regulatory agencies.

National Institute of General Medical Sciences

Ruth L. Kirschstein, M.D.,
Director
Sara A. Gardner, Ph.D.,
Director, Pharmacology
Research Associate Program

Pharmacology Research Fellowships

The National Institute of General Medical Sciences (NIGMS) has 11 positions (medical staff fellow and staff fellow) available each year for pharmacology research training. Those who are appointed begin on July 1 and are offered 2 years of postdoctoral training in a laboratory of a participating Institute of NIH under the Pharmacology Research Associate Program. The program seeks to develop scientists in pharmacologic research who will be leaders of the field in the future.

The program is directed to those persons who have already made a commitment in pharmacology by training or research in the field.

Fellows will engage in research relating principles of pharmacological sciences to contemporary biomedical problems. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, physics, and instrumentation is also available. During their tenure, pharmacology research fellows devote the larger portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities.

Professional growth is achieved through the process of personal guidance by senior NIH scientists who are preceptors. A variety of laboratory problems and research approaches are designed to advance the work in progress and the competence of the prospective independent investigator. Preceptors and research fellows are matched by a mutual selection procedure after personal interviews. Candidates for pharmacology positions include those who will have received either the Ph.D., M.D., or equivalent degree and have research experience in areas relevant to pharmacology. They may also include those with research experience in a related area but who wish to further their development in pharmacology. Applicants with an M.D. degree may use this opportunity to further their training in basic pharmacologic research in preparation for a career in clinical pharmacology or a related discipline. Many NIH Institutes participate in this pharmacology research fellowship program.

Clinical Pharmacology

An opportunity is available for research training specifically in the area of clinical pharmacology. Applicants for research training in clinical pharmacology should have the M.D. degree, a minimum of 1 year, preferably 2, of graduate medical training (internship, residency), and a demonstrated interest in clinical pharmacology. The successful applicant will participate in a developing 2-year program under the guidance of several groups of investigators who are actively engaged in clinical pharmacological research in the Clinical Center, NIH. These preceptors will include but are not limited to:

Bruce Chabner, M.D., Chief,
  Clinical Pharmacology Branch,
  National Cancer Institute
Michael Ebert, M.D.,Chief,
  Section on Experimental Therapeutics,
  National Institute of Mental Health
Stephen Epstein, M.D., Chief,
  Cardiology Branch, National Heart,
  Lung, and Blood Institute
James Gillette, Ph.D., Chief,
  Laboratory of Chemical Pharmacology,
  National Heart, Lung, and
  Blood Institute

Harry Keiser, M.D.,Clinical Director,
National Heart, Lung, and
Blood Institute
Irwin Kopin, M.D., Chief,
Laboratory of Clinical Science,
National Institute of Mental Health
Charles Myers, M.D., Chief,
Biochemical Pharmacology Section,
Clinical Pharmacology Branch,
National Cancer Institute
Daniel Nebert, M.D., Chief,
Developmental Pharmacology Branch,
National Institute of Child Health
and Human Development
Snorri Thorgeirsson, M.D., Ph.D.,
Laboratory of Carcinogen Metabolism
National Cancer Institute

William Z. Potter, M.D., Ph.D., intramural clinical pharmacologist, will serve as coordinator of the fellow's overall training in clinical pharmacology. The program emphasizes laboratory methods applicable to pharmacological research in man but also includes training in general clinical pharmacological principles (clinical pharmacokinetics and pharmacodynamics, biostatistics, drug evaluation, drug epidemiology, etc.).

The clinical pharmacology fellow's research experiences will be planned individually to meet the needs dictated by previous training, experience, and career goals. This research experience will involve both laboratory and human investigation.

A training plan, including formal course work, for each fellow will be developed by the Pharmacology Research Associate Program. A series of seminars will be organized with the participation of the clinical pharmacology fellows to ensure that their needs are met. Fellows may also help develop and instruct in the medical student elective program in clinical pharmacology.

In addition to a primary involvement in clinical pharmacological research, the fellow will participate in clinical pharmacology rounds. These rounds will be directed on an alternating basis by preceptors from the different categorical areas to ensure a broad exposure to a wide range of problems in clinical pharmacology. Part of the clinical pharmacology experience will be collaborating with the coordinator in clinical pharmacology consultations for the Clinical Center.

An applicant may be considered for both the regular pharmacology research fellowship program and the clinical pharmacology option. Further information may be obtained from the Pharmacology Research Associate Program, NIGMS, NIH, Westwood Building, Room 919, Bethesda, MD 20205.

Program Areas

Choice of program area depends on the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request as a preceptor any senior scientist at the NIH, with the approval of the Pharmacology Research Associate Advisory Committee. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities.

National Cancer Institute

Laboratory of Carcinogen Metabolism—
Snorri S. Thorgeirsson, M.D., Ph.D.

Investigations are conducted on: (1) the metabolic processing of various classes of chemical carcinogens, such as aromatic amines and amides; (2) the relationship between chemically induced mutations and carcinogenesis; (3) control of gene expression during chemically induced tumor formation; and (4) the role of modifiers of differentiation in the inhibition or promotion of tumor formation.

Clinical Pharmacology Branch—
Bruce A. Chabner, M.D.

Our laboratory is concerned with the mechanism of action, pharmacokinetics, and mechanisms of resistance for the antimetabolite classes of antineoplastic drugs. Our primary interest at present is the process of metabolic conversion of antifolic compounds to polyglutamate metabolites. This conversion produces an intracellular metabolite which has different pharmacokinetic and biochemical properties from the parent compound and which appears to extend the duration of action of the drug. We have also been concerned with the clinical pharmacology of methotrexate, specifically with the use of test doses to predict drug clearance and to modify the doses in patients who receive high risk forms of methotrexate therapy. Other projects which our laboratory has recently completed include studies of mechanisms of antifolate resistance in cloned human tumor cells, determinations of cytotoxicity for the cytidine class of antimetabolites (cytosine arabinoside), and the mode of action of fluoropyrimidines. We are also collaborating in studies of the role of the pineal hormone, melatonin, in determining the risk of development of breast cancer in experimental models. These studies of melatonin physiology are conducted in conjunction with Dr. Marc Lippman's laboratory (Medicine Branch) and Dr. Larry Tamarkin of the NICHD.

Laboratory of Experimental Therapeutics and Metabolism—

Michael R. Boyd, M.D., Ph.D.

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is in analytical and clinical pharmacology; qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents are studied in experimental systems, as well as in man in a clinical setting. Problems are selected for their relevance to the development and/or evaluation of new chemotherapy protocols, and frequently are pursued collaboratively with other NCI laboratories. The other major research area concerns the elucidation of fundamental chemicobiologic interactions underlying chemical-induced cytotoxicity and carcinogenicity to specific target organs and target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target tissue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic "activation" and "deactivation" systems are of interest as well as investigations of the biochemical, physiologic, and morphologic consequences of the *in situ* generation of alkylating metabolites both in normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemical-induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimal toxicity to normal tissues.

Laboratory of Medicinal Chemistry and Pharmacology—

David G. Johns, M.D., Ph.D.

This laboratory conducts an integrated program for the rational development of antitumor agents, carries out the synthesis of compounds with potential antitumor activity, and assesses the effects of such agents on experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites—nucleic acids, cell membranes, and microtubular protein and enzyme systems. Of special concern are agents that act as "stoichiometric" or "titrating" enzyme inhibitors, with current emphasis on the interaction of 2′-deoxycoformycin with adenosine deaminase and on the biochemical and pharmacologic effects of 2′-deoxycoformycin when used in combination with adenosine analogues. Another area of current interest is the maytansine group of mitotic inhibitors and the nature of their binding with microtubular protein.

- Drug Metabolism Section—
  Richard L. Cysyk, Ph.D.

This section is involved in studies of the metabolism, mechanism of action, and mechanism(s) of selective toxicity of antitumor agents. New drugs are designed, synthesized, and evaluated for their effects on biochemical pathways critical to cell survival. Drugs are tested for cytotoxicity using *in vitro* cell cloning techniques and for antitumor activity in animals with tumors. An emphasis is placed on identifying endogenous factors that alter drug toxicity and that influence differential drug toxicity. An area of current interest is the development of analytical methods using stable labeled compounds in combination with mass spectrometric techniques to study the flux through the *de novo* pyrimidine pathway *in vivo.* A goal of this research is to understand the regulation of *de novo* nucleoside synthesis in organs and tumors *in vivo.*

- Applied Pharmacology Section—
  Robert I. Glazer, Ph.D.

This section conducts studies of the mechanism of action of anticancer drugs in both mouse and human tumor cells in tissue culture. Areas receiving the greatest emphasis include the synthesis and processing of ribosomal, messenger, and transfer RNA; the methylation of RNA and DNA; the synthesis and repair of DNA and the metabolism of anticancer drugs by the tumor cell. The classes of drugs under investigation are nucleoside analogs, intercalating agents and human interferon. The primary purpose of these studies is to relate the cytotoxicity of anticancer drugs, as assessed by soft agar cloning, with their mechanism of action at the molecular level. A variety of the most up-to-date methods utilized in molecular biology and pharmacology are employed in successfully carrying out these avenues of investigation.

- Biochemical Toxicology Section—
  Theodore E. Gram, Ph.D.

Research interests include the chemical and biochemical mechanisms involved in interactions between xenobiotics and biologic materials that result in toxic responses; the morphologic reaction to toxic response to determine if the morphologic alterations precede, coincide with, or follow toxicity; studies to determine whether toxicity is spontaneously reversible and what factors, if any, augment or diminish the toxicity; and investigations on whether toxicity exhibits organ specificity and, if so, how it might be explained. The section is particularly interested in the role of drug oxidation and conjugation in the detoxication and toxication of xenobiotics. Past work has been oriented toward microsomal and cytosol enzymes of the liver, lung, and kidney in these phenomena. Studies with lung have been conducted in intact animals, the isolated perfused lung, slices from normal lung and lung tumors, tissue homogenates, and subcellular fractions. This group is also interested in the functions that tissue uptake, binding, metabolism, and clearance have in drug-related specific end-organ toxicity. Investigations are currently in progress to evaluate these questions since they relate to the serious and dose-limiting problems of pulmonary fibrosis associated with a number of oncolytic agents such as bleomycin, renal necrosis resulting from platinum compounds, and myocardial fibrosis associated with adriamycin.

- Molecular Biology and Methods
  Development Section—
  Marco Rabinovitz, Ph.D.

Attention is focused on the development of approaches for the potentiation of cancer chemotherapeutic activities. Nutritional and pharmacologic regimens are first explored in tissue culture and then extended to the tumor-bearing animal in attempts to direct cytotoxic agents toward the tumor cell and away from sensitive normal tissues. New cytotoxic and potentiating agents are also synthesized to achieve this goal. Biochemical studies include the analysis of inhibition kinetics of binding, transport, and detoxification of cytotoxic agents in sensitive and resistant tumor cells and in sensitive host tissues. An investigator is encouraged to use several of the above methodologies in pursuit of the solution to a particular problem.

- Pharmacokinetics and
  Pharmacodynamics Section—
  Daniel S. Zaharko, Ph.D.

This section is involved with pharmacologic investigations of cancer chemotherapeutic agents. Research efforts are currently directed toward altering the selectivity of known anticancer drugs by linking them to synthetic polymers and by using them in conjunction with normal intermediary metabolites such as nucleosides, amino acids, or vitamins. Most studies utilize rodent species and involve pharmacokinetics, radioactive tracers, techniques of cell growth, and soft agar cloning *in vivo* and *in vitro*.

The research interests of this section are the relationship between pharmacokinetics and drug effects, the biochemical selectivity of anticancer agents in different organs and tissues, and the transport and role of nucleosides in the biochemical balance of the whole animal.

National Heart, Lung, and Blood Institute

Cardiology Branch—
Stephen E. Epstein, M.D.

The branch's research objectives are oriented primarily toward an elucidation of the physiologic and biochemical mechanisms responsible for control of both the normal and failing heart, as well as the effects of various pharmacologic interventions on the normal and failing heart. Projects include pharmacologic, physiologic, and biochemical studies in man and animals. Major emphasis is on the study of the mechanisms responsible for myocardial cell death in acute myocardial infarction and in determining the causes of angina pectoris. Related studies are devoted to therapeutic interventions with particular emphasis on the effects of calcium channel blocking agents. Emphasis is also placed on study of the biochemical mechanisms involved in actin-myosin interaction and in muscle contraction.

Laboratory of Chemistry

- Section on Physiological Chemistry—
  John J. Pisano, Ph.D.

Normal and pathologic states in man are studied at the molecular level. Under investigation are neuroactive (enkephalins) and vasoactive peptides (bradykinin and angiotensin), precursor proteins of the peptides (kininogens), and the enzymes (kallikreins) involved in their biosynthesis and degradation. Modern analytic techniques such as gas chromatography, high-performance liquid chromatography, affinity chromatography, mass spectrometry, and radioimmunoassay are commonly employed. Research is currently directed toward the discovery of naturally occurring biologically active peptides, the study of hypertension, new factors regulating coagulation and fibrinolysis, and micromethods for the detection and amino acid sequence analysis of polypeptides.

Laboratory of Chemical Pharmacology—
James R. Gillette, Ph.D.

- Section on Drug-Enzyme Interaction—
  James R. Gillette, Ph.D.

Various aspects of drug disposition are investigated, including the relationship between drug metabolism and drug toxicity. The main objective of this section has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. This section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal level.

- Section on Cellular Pharmacology—
  Michael A. Beaven, Ph.D.

This section has an interest in the study of drug action at the cellular level. Current work includes: studies on the mechanism of repression of lymphocyte blast transformation by anti-inflammatory drugs; the inhibition of white cell recruitment and chemotaxis in inflammatory reactions by anti-inflammatory drugs; release and metabolism of histamine and other active factors during inflammatory and allergic reactions; and studies with purified populations of cells from the gastric mucosa and capillary endothelial cells to determine distribution of histamine receptors and biochemical responses to histamine and other active hormones.

- Section on Pharmacological Chemistry—Lance R. Pohl, Pharm.D., Ph.D.

This section studies the mechanisms of metabolism, action, and toxicity of pharmacologically active chemicals. Research under way includes studies aimed at identifying active substances formed in the body, determining the biochemical basis of their pharmacologic and toxicologic actions, and at characterizing the nature and regulation of the enzymes that either produce or metabolize these agents.

Hypertension-Endocrine Branch—

- Section on Biochemical Pharmacology—
  Walter Lovenberg, Ph.D.

Research is directed toward understanding the regulation of monoaminergic systems and the relationship of these systems to specific diseases. Both biochemical and pharmacologic approaches are used to investigate various neuronal systems and how information is transmitted between cells. This group is particularly interested in the role of cyclic nucleotides and calcium in these receptor-mediated responses. Some of the current research projects are: molecular characterization of the monoamine biosynthetic enzymes; regulation of catecholamine and serotonin synthesis by protein phosphorylation reactions; molecular events involved in the transduction of nerve impulses into changes in target cell proteins and enzyme levels in small blood vessels and the pineal gland; the distribution and physiologic role of the hydroxylase cofactor (tetrahydrobiopterin); the role of calmodulin in regulation of the activity of neuronal systems; the biochemical mechanism of antihypertensive and antipsychotic drugs; and the role of central and peripheral nervous systems in the regulation of blood pressure in experimental animals and man. The work encompasses several fields, including pharmacology, enzymology, protein chemistry, and molecular biology.

- Section on Biochemical Pharmacology—
  Ingeborg Hanbauer, Ph.D.

Ongoing work in this laboratory focuses on regulation of release of enkephalin-like peptides from adrenal glands. The effects of electrical stimulation of the splanchnic nerve, and those of specific agonists and antagonists of nicotinic or opiate receptors on the release of met-enkephalin-like peptides are investigated. The peptides released from the adrenal chromaffin cells into the adrenal venous blood are characterized by HPLC and RIA using specific antibodies.

Work is also focused on pharmacological and biochemical aspects of the regulation of striatal dopamine receptors. The regulation of adenylate cyclase-linked dopamine receptors is studied in corpus striatum with particular attention on two of its functional states, sub- and supersensitivity. These studies comprise measurements of dopamine recognition sites, G/F protein, responsiveness of adenylate cyclase to dopamine, modulator proteins (calmodulin) phosphorylation, and dephosphorylation of membrane proteins and protein kinases.

Laboratory of Biochemical Genetics—
Marshall W. Nirenberg, Ph.D.

- Section on Molecular Biology—
  Marshall W. Nirenberg, Ph.D.

Studies are conducted on clonal cells derived from the nervous system, including those of normal and neoplastic origin as well as somatic cell hybrids. The objectives of this section are to identify molecules and reactions that enable cells to communicate with each other and to investigate the problem of how genes determine synaptic circuits when neurons are assembled into circuits during embryonic development. Work predominantly involves biochemistry and enzymology, mammalian cell culture, cyclic nucleotide enzymology, cell receptors, and enzymes of neurotransmitter metabolism.

Research is also directed toward the mechanism of action of opiate peptides, dependence and tolerance to these compounds, and the relationship of opiate receptors in the regulation of adenylate cyclase activity.

- Section on Macromolecules—
  Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms. One area of interest involves a study of the hypothalamic tripeptide, thyrotropin-releasing factor. The biochemical and pharmacologic properties of a newly discovered metabolite of thyrotropin-releasing factor are under investigation. These experiments may lead to a better definition of the metabolism and mechanism of action of this hormone. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells. Current information suggests that cyclic AMP concentrations in *Escherichia coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells.

Laboratory of Cellular Metabolism—
Martha Vaughan, M.D.

The laboratory works on problems related to the control of cyclic nucleotide synthesis and degradation and the mechanisms of action of hormones and other agents that influence these processes in mammalian cells. Research in progress deals with cell-surface receptors, adenylate and guanylate cyclases, several cyclic nucleotide phosphodiesterases, cholera toxin, and ADP ribosyltransferases.

National Institute on Alcohol Abuse and Alcoholism

Laboratory of Preclinical Studies—
Forrest F. Weight, M.D.

Research investigations in this laboratory center around the pharmacology of neurons and synapses in the central and peripheral nervous system. The general areas studied include: cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin, and GABA; membrane mechanisms of neurotransmitter and drug actions; cellular actions of peptides such as enkephalins, endorphins, and LH-RF; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbiturates, opiates, and other neuroactive substances. The research techniques available to a medical staff fellow include: extracellular unit recording and iontophoresis of drugs and putative transmitters to single neurons in the CNS; intracellular recording and intracellular injection techniques; use of *in vitro* preparations, such as CNS slices, sympathetic ganglia, and tissue culture for studying the pharmacology of drug-receptor interactions; voltage and patch clamp techniques for studying the ionic basis of membrane permeability changes involved in drug and transmitter actions.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Laboratory of Bioorganic Chemistry—

- Section on Pharmacodynamics—
  John W. Daly, Ph.D.

This section is engaged in research on the formation, degradation, and role of cyclic nucleotides in the nervous system—mechanisms that control adenylate cyclase and phosphodiesterases, receptors for catecholamines and other neurotransmitters, the relationship of membrane potential and generation of cyclic nucleotides, the interrelationship of adenosine and calcium in the regulation of cyclic nucleotide formation and action, morphologic entities associated with cyclic nucleotide formation and action, and the effect of drugs on neuronal and muscular function, in particular the transport and function of ions such as sodium, potassium, and calcium.

- Section on Pharmacodynamics—
  Phil Skolnick, Ph.D.

The research program is concerned with understanding the relationship between receptors for psychoactive compounds and the endogenous substances which normally subserve these receptors. The techniques employed in studying these relationships range from biochemical investigations of the nature of endogenous ligands and their interaction with membrane receptors to the use of both primary and transformed cell culture models and classical "whole animal" pharmacology. Specific projects currently under investigation include: (1) differential regulation of CNS benzodiazepine receptors by pharmacologically defined "agonists" and "antagonists;" (2) study of the role of purines such as adenosine in modulation of central function through interaction with specific receptor sites; and (3) the physiologic and pharmacologic modulation of recognition sites and uptake systems in the CNS for psychoactive drugs (*e.g.* phenethylamines such as amphetamine) and the relationship to the functional role(s) of such sites.

- Section on Oxidation Mechanisms—
  Donald M. Jerina, Ph.D.

The primary interest of this section is the elucidation of the fundamental mechanisms by which drugs and environmental chemicals are transformed in the body. In many instances oxidative metabolism produces chemically reactive metabolites which are responsible for the cytotoxic, mutagenic, and carcinogenic activity of the drug substrate. Recent studies have been concerned with the roles of the cytochrome P-450 system and epoxide hydrase in the formation of mutagenic and carcinogenic metabolites from the polycyclic aromatic hydrocarbons. Emphasis is on modern instrumental techniques such as high-pressure liquid chromatography, high-resolution mass spectrometry-gas chromatography, and high-resolution magnetic resonance in the study of metabolism catalyzed by homogeneous enzymes.

Laboratory of Biochemical Pharmacology—
Herbert Tabor, M.D.

Work in this laboratory is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biologic materials and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Current work is directed toward the mechanism and *in vivo* significance of these effects. The studies provide experience with a variety of techniques (enzyme characterization, bacteriophage, nucleic acid chemistry, and isotopic and nonisotopic synthesis). Special emphasis is placed in the use of plasmids and techniques involving DNA cloning, as well as on various genetic techniques in both *Escherichia coli* and in yeast.

Other work includes studies on control mechanisms for other enzymes in bacteria and in mammalian cell culture, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability. Studies are also carried out on developmental biology and organ regeneration in the rat and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation. Other studies involve the biology and immunology of the complex carbohydrates of animal cell surfaces.

- Loretta Leive, Ph.D.

This laboratory studies how structure is related to function in biological membranes. Phagocytosis in macrophages is being studied with two approaches: First, mutants of permanent macrophage cell lines unable to phagocytose have been selected and the biochemical changes responsible for these defects are being studied. Second, we have found that phagocytosis of bacteria by macrophages can be affected by slight changes in structure of bacterial surface polysaccharide; the effect of such changes on interaction with macrophages either directly or via complement activation is being studied. Bacterial membrane function is also being studied, specifically the outer membrane of gram-negative bacteria. This membrane admits small hydrophilic molecules but excludes larger hydrophobic ones, which is the opposite of most known biological membranes. Mutants altered in outer membrane components, or with increased permeability, are being used to analyze the mechanisms involved. Since exclusion of hydrophobic molecules causes resistance of gram-negative bacteria to antibiotics, the results may suggest ways to increase bacterial drug sensitivity.

- Section on the Genetics of Simple Eukaryotes—
  Reed B. Wickner, M.D.

We are studying the genetic control of replication of a set of double-stranded RNAs found in virus-like particles in the simple eukaryote *Saccharomyces cerevisiae* (yeast). These double-stranded RNAs determine the "killer trait," the production of a toxin lethal to yeast not carrying the virus. We have found that replication of the double-stranded RNA genome involves a large number of chromosomal genes, several genes on the double-stranded RNA segments themselves, and a mitochondrial gene. These components show many complex functional interactions. Current work to examine the nature of these genes and the mechanisms of their interactions involves genetics, enzymology, pharmacology, molecular cloning, and molecular biology.

Laboratory of Biochemistry and Metabolism—
William B. Jakoby, Ph.D.

This group approaches the problems of detoxication at the level of purified enzymes. Proteins are brought to the stage of homogeneity and are studied with respect to catalytic, binding, and regulatory properties. Emphasis is on the mechanism of action of those enzymes catalyzing conjugation reactions with glutathione or adding sulfate or methyl groups. Currently, a natural inhibitor of methylation is being evaluated at both enzyme and cell culture level.

Laboratory of Cell Biology and Genetics

- Section on Cell Biology and Biochemistry—
  Harvey B. Pollard, M.D., Ph.D.

The primary interest of this group is in mechanisms of secretion of proteins, hormones, peptides, and transmitters from neuroendocrine and other cells. The systems we are particularly interested in include chromaffin cells, islets of Langerhans, platelets, and synaptosomes. Critical problems now under investigation include how secretory vesicle assembly is regulated, how cytoskeletal proteins interact with subcellular organelles, how calcium acts to fuse secretory vesicles to plasma membranes, and how the release of vesicle contents during exocytosis subsequently occurs. The approach of this laboratory is to search for special proteins that could mediate such events; at present these include actin. synexin, a new protein that fuses secretory vesicle membranes exclusively in the presence of calcium, and synhibin, a protein which regulates synexin. The interactions of these and related proteins with a wide variety of pharmacologic and environmental agents known to affect secretory processes are being analyzed.

Diabetes Branch—
Jesse Roth, M.D.

The Diabetes Branch studies receptors for peptide hormones, especially insulin, insulin-like growth factors, and growth hormone. Current projects are focused on the role of receptors and receptor antibodies in disease states, genetic disorders of the insulin receptor, biosynthesis of receptor components, the role of receptors in hormone action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects include insulin and insulin receptors in the central nervous system; the evolutionary origin of insulin, ACTH, somatostatin, and other peptide messenger molecules; and their role in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

National Institute of Child Health and Human Development

Laboratory of Developmental Neurobiology—

Phillip G. Nelson, M.D., Ph.D.

Research is conducted in neurobiology with the use of tissue cultures of normal and neoplastic nerve and muscle and various invertebrate preparations. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress. The membrane mechanism of action of such neuroactive peptides are under investigation. A primate vocal communication system in the squirrel monkey is being analyzed in behavioral and etiologic terms and with neurophysiologic techniques.

- Section on Intermediary Metabolism— Gordon Guroff, Ph.D.

Investigators in this section are interested in the biochemical and physiological actions of nerve growth factor. This factor has been studied for many years and its function is now clear; it is required for the development and survival of the sympathetic and sensory nervous systems. Without nerve growth factor, these neurons die. The chemistry of nerve growth factor has been completely elucidated, but its mechanism of action, and indeed the mechanisms of action of the more than 30 other growth factors now known, are only dimly perceived.

Our work involves a dissection of the biochemical events which follow the interaction of nerve growth factor with the cell, particularly those in the nucleus. The systems we use are organ cultures of sympathetic ganglia from neonatal animals and the PC12 cell, a pheochromcytoma clone which differentiates *in vitro* into a sympathetic neuron in response to nerve growth factor. Within recent years, it has become clear that phosphorylative changes in the proteins of these cells are pivotal events in the actions of the factor. We are involved in the isolation and purification of the proteins involved and of the enzymes carrying out these phosphorylations, as well as in studies aimed at understanding the role of these proteins in the structure and transcription of DNA. The ultimate goal is to define the exact molecular mechanism of these peptide factors. We also have ongoing research on the induction of transmitter-synthesizing enzymes, the relationship of the sympathetic nervous system and the immune system, the enzymology of neurite development, and the actions of growth factors on the central nervous system.

- Section on Neuroendocrinology— David C. Klein, Ph.D.

Investigations within the section focus on the molecular mechanisms through which hormones and biogenic amines regulate gene expression, with the primary experimental model being cultured pineal cells. Research is concerned with the relationship between biogenic amines and the production and release of hormones; emphasis is given to the study of β-adrenergic control of cyclic AMP and α-adrenergic control of cyclic GMP in pineal cells, and how these systems control metabolism. In addition, enzyme induction and activation is studied using drugs as biochemical and electrophysiologic tools to understand the intracellular reactions involved in large changes in enzyme activity. A second major area of interest is the factors regulating circadian rhythms; current investigations are concerned with the central neural mechanisms involved in generating daily rhythms in primates.

Laboratory of Theoretical and Physical Biology—

David Rodbard, M.D.

This laboratory utilizes a variety of biophysical methods, including nuclear magnetic resonance, mass spectrometry, and pharmacokinetic modeling, to study the metabolism of calcium, other metals, carbohydrates, steroids, and amino acids in man. The Section on Metabolic Analysis utilizes safe (nonradioactive) stable isotopes to study metabolic correlates of growth, development (e.g., the effects of growth hormone and sex steroids), and pregnancy in human subjects. The Section on Molecular Pharmacology utilizes nuclear magnetic resonance (NMR) spectrometry to study metabolism at the cellular level, and to study DNA conformation in relation to drug and protein binding. The Section on Theoretical Biology employs mathematical modeling, artificial intelligence, and statistical methods for computerized dose adjustment programs and other applications. Drug receptor interactions (e.g., bivalent enkephalins, benzodiazepines) are studied in the laboratory and with computer modeling.

Fellows will be trained in techniques of clinical investigation, and in the relevant laboratory, biophysical, and computer methods, in accord with their individual research background, interests, and objectives.

Laboratory of Neurochemistry and Neuroimmunology—
Harold Gainer, Ph.D.

This laboratory investigates the biosynthesis, secretion, and mechanisms of action of various biologically active neuropeptides. These peptides include ACTH, and α-MSH, β-endorphin, dynorphin, vasopressin, and oxytocin. Techniques employed include immunochemistry and assay, immunocytochemistry, recombinant DNA methodology, protein and peptide separation and chemistry, and microchemistry of small brain areas. The laboratory uses a cell-biological approach to the intracellular and extracellular mechanisms which determine the expression of specific neuronal identity (i.e., its endogenous peptides, its particular projection pathways, and its specific termination sites in the central nervous system). The interactions between catecholamine and peptide synthesizing neurons in the nervous system are studied.

Developmental Pharmacology Branch—
Daniel W. Nebert, M.D.

This branch investigates the interplay between genetic and environmental factors affecting drug-metabolizing enzymes. Molecular genetics and recombinant DNA technology are used to exploit the genetic regulation of drug-metabolizing enzymes among inbred mouse strains and in cultured cells. The induction of these enzymes by drugs and other environmental agents, combined with underlying genetic predisposition of the individual animal, produce diverse responses seen in the research areas of pharmacology, toxicology, teratology, and chemical mutagenesis and carcinogenesis. The induction process involving drug receptor is also under study. Data obtained from these experimental test systems are used to develop assays for predicting who is at increased risk for environmental diseases among human populations.

National Institute of Dental Research

Neurobiology and Anesthesiology Branch—
Ronald Dubner, D.D.S., Ph.D.

This branch conducts studies on the neural basis of somatic sensation with an emphasis on pain mechanisms. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions. Electrophysiologic studies are concerned with the functional characteristics of single cells in the dorsal horn and their role in the coding of pain, temperature, and tactile information. In behavioral studies, monkeys are trained to discriminate noxious and innocuous thermal stimuli, and behavioral events are correlated with single-unit activity in the dorsal horn. The effects of various chemical mediators in brain on neural function and animal behavior are studied utilizing this behavioral model.

The clinical program of this branch conducts research on pain assessment and evaluates various pharmacologic agents utilized in the control of acute and chronic pain. Present studies include the development of new verbal descriptor methods for measuring experimental and clinical pain, the role of endogenous opiates in the control of postsurgical pain, the efficacy and toxicity of intravenous sedation methods used for ambulatory surgical procedures, and clinical trial studies on the analgesic potency of nonsteroidal anti-inflammatory drugs.

National Institute of Environmental Health Sciences

This Institute is the only one of the 11 Institutes that comprise the National Institutes of Health that is not situated on the campus in Bethesda, Maryland. It is located in Research Triangle Park, North Carolina.

Laboratory of Environmental Biophysics—
Colin F. Chignell, Ph.D.

Research programs of the laboratory cover two main areas—the biological effects of some of the physical factors (nonionizing radiation, noise, and light) present in the environment and the use of physicochemical techniques to monitor the interaction of chemical and physical agents with various biological systems. The aim of the nonionizing radiation program is to develop new microwave exposure systems and to determine the effect of microwave exposure on human health. Current efforts include the effect of microwave radiation on the central nervous system and animal behavior, the cardiovascular system, the immunologic defense systems, and the fetus. The major effort of the noise program is directed towards elucidating basic mechanisms of noise-induced hearing loss, providing better methods for assessing such losses, and providing the means for accurately reproducing specific noise exposure environments. The remainder of the effort is focused on the reproductive, teratogenic, cardiovascular, and behavioral effects of noise. The light program is concerned with the mechanism of chemically induced photosensitivity and photoallergy. The effect of light of different wavelengths on the behavior and response of experimental animals to chemical agents is also being examined. The program in molecular biophysics mainly focuses on the use of sophisticated spectroscopic techniques (ESR, NMR, fluorescence and absorption spectroscopy, CD) to monitor the interaction of environmental agents with biologic systems. Current studies include the generation of free-radical intermediates during this metabolism of xenobiotics, the mechanism of mast cell degranulation, the binding of dyes to nucleic acids, and the interaction of metal ions with proteins and membranes.

Laboratory of Pharmacology—
James R. Fouts, Ph.D.

The research programs of this laboratory are concerned with relationships between the metabolism and translocation of chemicals and toxicity in various target organs. Pharmacologic, biochemical, physiologic, and pharmacokinetic concepts are used to elucidate the mechanisms by which environmental contaminants exert their toxic effects. Special areas of emphasis are: (1) those enzyme systems involved in the formation and detoxication of reactive metabolites, such as epoxides. An integrated approach is used in these studies and experiments are performed with purified enzymes (e.g., various cytochromes P-450), enriched cell populations isolated from several organs, isolated perfused organs, and intact animals; (2) the mechanisms whereby chemicals with hormonal activity alter the normal functions of liver; (3) the role of membrane structure and function in excretion and toxicity of environmental pollutants; and (4) the elucidation of reliable endpoints for the extrapolation of dose-dependent chemical effects across animal species and to humans.

The Laboratory of Pharmacology also serves as a focal point within NIEHS for marine and freshwater biomedical research. This program is especially interested in the direct impact of pollutants present in the aquatic environment (including drinking water and aquatic animals) on human health. Mechanistic aspects of the accumulation, biotransformation, excretion, and toxicity of contaminant chemicals are studied in aquatic vertebrate and invertebrate species, and are compared to similar processes in mammals. John B. Pritchard, Ph.D. heads a program that is situated at the C. V. Whitney Marine Laboratory of the University of Florida near St. Augustine.

Laboratory of Reproductive and Developmental Toxicology—
Robert L. Dixon, Ph.D.

Scientific efforts are directed toward the understanding of mechanisms of reproductive, endocrinologic, and developmental toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis using *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratogenic potential; determine the molecular mechanisms underlying cellular differentiation; study the molecular basis and determine the effects of environmental agents on endocrine function; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects which do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of reproductive, endocrinologic, and developmental toxicity using *in vitro* cells and tissues, lower animals, and biochemical test systems.

- Experimental Teratogenesis Section—
  Robert M. Pratt, Ph.D.

Studies in this section deal primarily with embryonic and fetal development and with the mechanism by which various environmental agents and drugs interfere with normal development. Emphasis is placed on the development of the craniofacial region and the biochemical and molecular basis for sensitivity to teratogens using cell, organ, and whole embryo culture in conjunction with biochemical, morphologic, pharmacologic, and toxicologic approaches. Of special interest is the manner in which various hormones and growth factors influence normal and abnormal development of embryonic and fetal tissues. Also of interest are the biochemical and molecular factors predisposing various strains of mice to the teratogenic and toxicologic effects of agents such as steroids and dioxins (TCDD).

Laboratory of Behavioral and Neurological Toxicology—
Clifford L. Mitchell, Ph.D.

The research programs of the Laboratory of Behavioral and Neurological Toxicology cover three broad areas—the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurologic abnormalities, studies concerning the mechanism whereby environmental factors produce their behavioral and neurotoxic effects, and studies concerning the conditions that alter the responsiveness of individuals to the behavioral and neurologic effects of environmental factors. An interdisciplinary approach to these problems is taken utilizing behavioral, neurochemical, neurophysiologic, and neuropathologic techniques. Particular emphasis is placed on the behavioral and neurologic effects resulting from exposure to environmental agents during the development of the nervous system. Among the substances being studied are heavy metals, halogenated hydrocarbons, volatile solvents, microwaves, and their interactions with psychoactive drugs.

Laboratory of Pulmonary Function and Toxicology—
Paul Nettesheim, M.D.

The research programs of the Laboratory of Pulmonary Function and Toxicology are concerned with the study of the cellular and biochemical basis of normal and abnormal lung functions. Special areas of emphasis are:
(1) regulation of biosynthesis and secre-

tion of mucus glycoproteins; (2) metabolism of prostaglandins in the lungs and the effect of prostaglandins on some metabolic functions of the lung; (3) the composition, secretion, and function of the noncellular alveolar lining layer, particularly its protein components, and disturbances of the acellular alveolar lining layer in disease; (4) the biology, life cycle, and function of respiratory tract epithelial cells studied with *in vivo* and *in vitro* techniques; (5) the mechanisms of toxicity of airborne particles and fibers on lung tissues and the mechanisms of toxicity of asbestos studied *in vivo* and *in vitro*; and (6) mechanisms of respiratory tract carcinogenesis, the development of neoplastic disease, *in vitro* epithelial cell transformation and promotion studies, and mechanisms of cocarcinogenesis and promotion.

National Institute of Mental Health

Laboratory of Clinical Science—

- Section on Pharmacology—
  Julius Axelrod, Ph.D.

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory also engages in examining control mechanisms of the biochemistry of the pineal gland, methylation reactions, and membrane structure and function.

- Section on Pharmacology—
  Juan M. Saavedra, M.D.

The current research program is centered on two areas. One relates to the central mechanisms involved in the control of cardiovascular function and the development of high blood pressure. A combination of microanatomical techniques, radioenzymatic assays, and radioimmunoassays is used to study the metabolism of biogenic amines and neuropeptides in selected brain areas of several animal models of experimental and genetic hypertension.

The second area of interest relates to the role of biogenic amines and neuropeptides in anterior, intermediate, and posterior pituitary function. Both experimental and genetic animal models are used. Current research is focused on the role of protein carboxylmethylation in the mechanism of vasopressin release, the interactions between biogenic amines, vasopressin and other neuropeptides in the posterior pituitary, and the interactions between somatostatin, MSH, estrogens, and catecholamines in the intermediate pituitary lobe.

- Section on Histopharmacology—
  David M. Jacobowitz, Ph.D.

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic), cholinergic, gabaminergic, and peptidergic neurons in the brain, and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical, neurochemical, and physiologic analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying basis for behavioral changes. Catecholamine histofluorescence, immunofluorescence, drugs, stress, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Neuronal amines, enzymes, proteins, and peptides are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence methods are also being used to study the localization of enzymes (DβH) and peptides (α-MSH, CRF, secretin, enkephalin, substance P, pancreatic polypeptide) in the brain.

- Section on Medicine—
  Irwin J. Kopin, M.D.

The research efforts of this section are centered around the study of biochemical and physiologic effects of drugs and toxins that alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes that control their synthesis in the central and peripheral sympathetic nervous systems. The techniques used include radioisotopic methods (*in vivo* and *in vitro*), tissue slices, perfused organs, and organ and tissue cultures. Brain lesions and chronic indwelling catheters placed in arteries, veins, and cerebral ventricles are used in studies on animals. For application to clinical studies, procedures are developed to evaluate neurotransmitter and neuroendocrine function in human subjects with various neuropsychiatric disorders or during administration of psychoactive drugs. Plasma, urine, and cerebrospinal fluid are analyzed for various drugs, amines, and metabolites, and the rates of utilization or synthesis determined using radioimmunologic, enzymatic, high performance liquid chromatographic or mass spectroscopic techniques.

Laboratory of Cell Biology—

- Unit on Biochemical Pharmacology—
  Martin Zatz, M.D., Ph.D.

Current work is on problems in two areas: one concerns the mechanisms by which circadian rhythms are generated and regulated. The other concerns the identification, biosynthesis, and physiologic role of nonpolar methylated lipids in membranes. Related areas include regulation of sensitivity, cyclic nucleotides, photoreception, and the pineal gland. Biochemical and pharmacologic approaches to these problems are emphasized.

- Michael J. Brownstein, M.D., Ph.D.

My colleagues and I are trying to locate peptidergic neurons in the CNS and to characterize them anatomically. In addition, we want to learn how peptidergic neurons synthesize, transport, store, and release their biologically active products and hope to show how these processes are regulated by hormones and neurotransmitters.

Laboratory of Cerebral Metabolism—

- Section on Developmental
  Neurochemistry—
  Louis Sokoloff, M.D.

Laboratory investigations are directed toward the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry to whole-animal physiology. Present emphasis is on the applications of a method recently developed in this laboratory that permits measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pathologic states.

Laboratory of Preclinical Pharmacology—
Erminio Costa, M.D.

This laboratory conducts a program of research in neurochemical pharmacology directed to elucidate the molecular mechanisms that regulate production, metabolism, and action of various putative neurotransmitters and the mode of action of various psychoactive drugs. Current research includes: the molecular regulation of postjunctional receptors for catecholamines, serotonin, GABA, acetylcholine, and polypeptides; the modification of the interactions between the neurotransmitters and endorphins and other neuropeptides elicited by long-term treatment with drugs; the use of stable isotopes to measure the turnover rate of acetylcholine, norepinephrine, dopamine, serotonin, and GABA by mass fragmentography in brain nuclei; the study of the mechanisms involved in the transsynaptic regulation of gene expression in neural cells; and the study of the heterogeneity of polypeptide neuromodulators in central and peripheral stores as an approach to understanding the regulation of their dynamic equilibrium.

- Section on Biochemical Pharmacology—
  Norton H. Neff, Ph.D.

The concern of this section is with the effect of drugs on the biochemistry and physiology of the nervous system. Emphasis is placed on the biogenic amine-containing neuron. Current studies are directed toward the characterization of enzymes involved in amine metabolism, the biochemical evaluation of receptor responses, the evaluation of the mechanism of action of drugs that alter neuronal function, and the possible role of the biogenic amines in various disease states.

Laboratory of Neurochemistry—
Seymour Kaufman, Ph.D.

The main effort of this laboratory is devoted to the metabolic interaction between the brain and its peripheral environment. Current research involves: 1) molecular characterization of phenylalanine, tyrosine, and tryptophan hydroxylases, enzymes that are rate limiting in the catabolism of phenylalanine and the biosynthesis of catecholamines and serotonin, respectively; 2) investigation of the regulation of these enzymes by cyclic nucleotide and calcium-dependent protein phosphorylation; 3) studies on the regulation of tetrahydrobiopterin biosynthesis, and the elucidation of physiologic roles for this compound other than as the essential cofactor for the aromatic amino acid hydroxylases mentioned above; 4) evaluation of the efficacy of pterin administration as therapy for human subjects with disorders of tetrahydrobiopterin metabolism; and 5) determination of the biochemical basis for hypertrophy of muscle, a tissue that shares many cellular characteristics with brain. This work encompasses numerous fields including pharmacology, enzymology, protein chemistry, pterin chemistry, and physiology. In use are techniques as diverse as affinity chromatography, HPLC, brain lesions, and indwelling catheterization of veins and arteries. Experimental preparations include tissue slices, synaptosomes, organ and tissue cultures, and hepatocytes as well as purified enzymes.

Laboratory of General and Comparative Biochemistry—
Werner A. Klee, Ph.D.

The major emphasis of the current program is directed toward the elucidation of the mechanism of action of opiates and the peptides that normally interact with opiate receptors. Included are studies on the isolation and characterization of opiate receptors and the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in culture, are aimed at understanding opiate tolerance and dependence in biochemical terms. In addition, the interrelationships among the several components of inhibitory-receptor adenylate cyclase couples, including especially GTP binding and hydrolysing proteins, are being explored. The relevance of this work to the action of other CNS-active drugs and to normal brain function is also being explored.

Biological Psychiatry Branch—
Agu Pert, Ph.D.

This laboratory is concerned with analyzing the mechanisms of action of psychoactive drugs and neuropeptides in the brain and defining the neurochemical coding of brain circuits that control specific behaviors. Methods used include extracellular single-cell recording as well as iontophoretic techniques with drugs in specific brain regions. Lesion and microinjection procedures are then utilized to relate these effects to behavior. Our current emphasis is on two projects: the actions of endorphins and enkephalins on brain function, especially the processing of pain information, and the effects of lithium (a therapeutic agent in manic-depressive illness) on neurotransmitter receptors sensitivity.

Clinical Neuroscience Branch
Steven M. Paul, M.D.

- Section on Preclinical Studies—
  Steven M. Paul, M.D.

The major research interests of the section concern the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with neuronal membranes, including membrane receptors and ion channels. Wherever possible basic laboratory studies are applied to behavioral and clinical problems. Several receptor systems are currently under investigation, including receptors for benzodiazepines, tricyclic antidepressants, serotonin, adenosine, and the neuropeptide cholecystokinin. The role and regulation of these systems are investigated by: (1) biochemical and pharmacologic characterization of the recognition sites; (2) isolation and characterization of the endogenous modulators of these sites; (3) development of appropriate *in vitro* models for studying these receptors (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharmacologic experiments in animals; (6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor changes in correlation to the behavioral manifestations of these genetic mutations; and (7) postreceptor events, including calcium transport and cyclic nucleotide changes.

- Section on Brain Biochemistry
  Candace B. Pert, Ph.D.

It has recently become apparent that neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell surface receptor. We use radiolabeled ligands with fully preserved biological activity to study drug and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain where neuroanatomical relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus with emphasis on identifying opiatergic neurocircuitry, systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (e.g. angeldustin, bombesin, substance P, neurotensin, and CCK) are also being studied. In short, the thrust of our laboratory efforts is the characterization, measurement, visualization, and solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally.

National Institute of Neurological and Communicative Disorders and Stroke

Developmental and Metabolic Neurology Branch—

- Membrane Biochemistry Section—
  Peter H. Fishman, Ph.D.

Our research involves the biosynthesis, organization, and function of cell surface membrane components. Of major interest are the mechanisms by which cells receive, process, and attenuate external signals. We are using the hormone-stimulated adenylate cyclase system as a model for transmembrane signaling. Hormones are recognized by specific receptors on the external side of the plasma membrane; following hormone binding, there is a transduction process which leads to stimulation of adenylate cyclase on the cytoplasmic side of the membrane. Prolonged stimulation results in desensitization whereby the transduction process becomes attenuated and in down-regulation whereby the receptors become internalized and degraded. We are also exploring the biosynthesis of two classes of receptors, glycoproteins and glycolipids; how these receptors become integrated into the plasma membrane; how the receptors are turned over; and how the cell regulates these processes.

Experimental Therapeutics Branch—

- Biochemical Neuropharmacology
  Section—John W. Kebabian, Ph.D.

The Biochemical Neuropharmacology Section studies the biochemical mechanisms underlying the activity of receptors for neurotransmitters. There is a special interest for dopamine receptors found in brain and simpler peripheral endocrine tissues. In the recent past, the section has studied the D-2 dopamine receptor in the intermediate lobe of the rat pituitary gland. The knowledge obtained from simple endocrine tissues about the biochemical mechanisms underlying receptor function has been applied to the brain.

- Physiological Neuropharmacology Section—
  Judith R. Walters, Ph.D.

Studies in the Physiological Neuropharmacology Section are focused on investigation of neuronal interrelationships and drug interactions with neurotransmitter function in the CNS, especially in areas of the basal ganglia, including the substantia nigra, striatum, and globus pallidus. Extracellular single unit recording procedures and iontophoretic techniques are chiefly employed; brain slice preparations are being established. Currently, the functions of dopamine, GABA, and peptide-containing neurons in these brain regions are being investigated through neurophysiologic determinations combined with drug treatment, administration of selective lesions, and assessment of biochemical parameters of transmitter function.

Laboratory of Neuropathology and Neuroanatomical Sciences—

- Section on Cellular Neuropathology
  Henry DeF. Webster, M.D.

This section uses morphological, immunocytochemical, virologic, biochemical, and immunologic methods to study cellular mechanisms of myelin formation, maintenance and breakdown. Special emphasis is placed on how these mechanisms relate to the diagnosis and pathogenesis of human demyelinating diseases. The section also investigates drugs and toxic agents that affect myelin sheaths and myelin-forming cells.

Laboratory of Neurophysiology—
Jeffery L. Barker, M.D., and Thomas G. Smith, Jr., M.D.

The principal aim of this laboratory is a multidisciplinary analysis of the cellular properties of specific CNS neurons and the pharmacologic effects of clinically important drugs on these properties. Most of the research is conducted using monolayer cultures of neurons dissociated from different regions of the mebryonic CNS. The methods employed are primarily electrophysiologic, including intracellular recording, voltage-clamp, and patch-clamp techniques, although other methods, including biochemical and morphologic, are also utilized. Specific projects include the comparison of chemically and electrically excitable membrane properties in CNS neurons and the effects of clinically important drugs on these properties, the identification of specific cell types using immunohistochemical and biochemical methods, and the separation of specific populations of neurons using cell sorting techniques.

National Institute of Mental Health

Herbert Pardes, M.D.,
Director
Frederick K. Goodwin, M.D.,
Director, Intramural Research
Irwin J. Kopin, M.D.,
Associate Director for Clinical Research
Michael H. Ebert, M.D.,
Clinical Director

The National Institute of Mental Health (NIMH) offers an opportunity for postdoctoral research training in psychiatry and in the biologic and behavioral sciences. The NIMH intramural program is located on the NIH campus in Bethesda, Maryland, and in the William A. White Building, St. Elizabeths Hospital, Washington, D.C. Some medical staff fellows conduct clinical and/or basic research, and are responsible for the clinical care of patients admitted for research and therapeutic purposes. Other fellows engage primarily in laboratory research in the biologic or behavioral science laboratories under the preceptorship of the senior staff. All medical fellows participate in tutorial seminars and other teaching programs as their needs and desires indicate. Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all medical staff fellows to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Appointments in Clinical Research

The NIMH recruits about 12 new medical staff fellows each year who are primarily involved in laboratory research. Appointments normally begin July 1 and are usually for 2- or 3-year periods, although in some instances they may be extended.

Fellows usually begin their appointments after the PGY-4 level of residency training. Well-qualified individuals, however, may be appointed after PGY-2 or PGY-3 levels of residency of training in psychiatry, neurology, or other clinical specialities. The Clinical Center is approved for 1 year of psychiatric residency training at the PGY-4 level.

Applications for the Medical Staff Fellowship Program are now being accepted only for July 1985 appointments. Since selections for these positions will be made in January 1984, PGY-2 or PGY-3 psychiatric residents may now apply.

Medical staff fellows usually work in close association with senior clinician-scientists on one of the clinical research wards or in a clinical research laboratory. The first year is usually predominantly clinical with intense experience in the diagnosis and inpatient management of research patients, special clinical and administrative issues in a research setting, psychopharmacology, clinical research methodologies and design (by the initiation of at least one clinical research project under the direction of the senior clinician-scientist), and the psychotherapy and psychodynamics of research patients and their families. The following years focus primarily on research that may be clinical, clinical-biochemical, or laboratory, depending on the interests of the fellow and the status of the clinical research program. Intensive clinical supervision on the inpatient psychiatric unit is available from senior psychiatrists and consulting psychoanalysts. Candidates desiring more information about clinical fellow positions should write to Michael H. Ebert, M.D., NIMH, Building 10, Room 3N234, National Institutes of Health, Bethesda, MD 20205.

Appointments in Laboratory Research

Some fellows work primarily in the laboratory under the preceptorship of a senior staff scientist. They are usually assigned to a basic science laboratory for intense training and experience in specific neurobiologic or psychosocial concepts and methodologies. For further information about these positions in the neurobiologic area, contact Irwin Kopin, M.D., NIMH, Building 10, Room 2D46, National Institutes of Health, Bethesda, Maryland 20205. For information in the psychosocial area, contact Marian Yarrow, Ph.D., NIMH, Building 15K, National Institutes of Health, Bethesda, MD 20205.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIMH programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in preclinical or clinical pharmacology. For more information about the PRAT program, see page 82.

Biological Psychiatry Branch—
Robert Post, M.D., Acting

This branch conducts a broad program of research, training, and treatment of clinical psychiatric problems including manic-depressive and schizo-affective illness, panic-anxiety disorders, menstrually related mood disorders, and suicidality. The focus of the branch is psychobiologic and brings together information from the following disciplines—psychiatry, psychology, neurology, genetics, pharmacology, and biochemistry. Longitudinal evaluation of the course of illness and response to treatment is an important clinical and research methodological approach. Some specific research interests are psychogenetics, the biochemistry of neurotransmission, neuroendocrinology, investigations of perception and cognition, cerebral tomography of average evoked potentials, and positron tomography. A general goal of this branch is to develop programs to investigate psychologic, biochemical, and neuroanatomic contributions to the study of manic-depressive illness, anxiety disorders, and related symptoms.

Fellows will be trained in clinical research methodology, data analysis, and clinical management of research patients.

- Section on Psychogenetics—
  Elliot S. Gershon, M.D.

A research goal of this section is to identify familially transmitted biologic and behavioral characteristics, including pharmacogenetic and inherited biologic vulnerability markers, that are associated with the affective and other major psychiatric disorders. The section has a followup outpatient clinic, a neurosciences and cell culture laboratory, and a recombinant DNA molecular genetics laboratory. An active program in biomathematics and genetic modeling studies of childhood risk and protective factors, and studies of new biologic treatments for affective illness in childhood and adulthood are ongoing.

- Section on Psychobiology—
  Robert M. Post, M.D.

This 14-bed psychiatric research unit focuses on the clinical and biologic assessment and treatment of patients with manic-depressive and schizoaffective illness and rapidly cycling phenomena. Medical staff fellows are research collaborators in a variety of studies of the interactions of psychological and biologic parameters in the psychoses and usually take responsibility for the design, conduct, and publication of several research projects. Mood, cognitive, and behavioral variables are viewed in relation to such biologic correlates as sleep, motor activity, evoked potentials, and endocrine function. Particular attention is given to the study in psychiatric patients of central amine metabolism with the use of CSF strategies, such as the measurement of amine metabolites, cyclic nucleotides, regulatory enzymes, and peptides in CSF. Work is closely coordinated with several biochemical laboratories. The mechanisms and time course of the biologic effects of psychotropic drugs are studied in relation to clinical response.

New pharmacologic agents are being tested, including noradrenergic receptor agonists, anticonvulsants such as carbamazepine, and several endogenous polypeptides. The mechanisms underlying the paradoxic antidepressant effect of one night's sleep deprivation are being studied. Clinical and laboratory studies of psychomotor stimulants are ongoing. An active behavioral pharmacology laboratory is maintained for the study of the long-term effects of psychomotor stimulant administration and electrical kindling in rodents and primates as models for the development of psychosis.

- Unit on Anxiety and Affective Disorders—Thomas W. Uhde, M.D.

This unit is engaged in the clinical and laboratory study of patients with anxiety and affective disorders. Most clinical research is conducted in the new Ambulatory Care Research Facility (ACRF), although intensive diagnostic assessment and drug treatment is available to patients on the 14-bed inpatient unit of the Biological Psychiatry Branch. A major emphasis is on the phenomenology, life course, familial patterns, and psychobiology of panic disorder, including agoraphobia with panic attacks. Particular attention is given to the study of possible "state" or "trait" markers of pathological anxiety and the testing of new anxiolytic agents. Current biologic correlates of interest include galvanic skin response, evoked potentials, sleep architecture, pain sensitivity, ^{3}H-imipramine and ^{3}H-dihydroergocryptine binding to the platelet and the neuroendocrine responses to agents with relatively selective effects on noradrenergic and other neurotransmitter systems. Drugs currently under study include alprazolam, caffeine, carbamazepine, clonidine, diazepam, propranolol, RO 15-1788, and yohimbine.

- Section on Neuroendocrinology—Philip W. Gold, M.D.

Neuroendocrine strategies for the evaluation of hypothalamic-pituitary function are developed, and these measures are integrated with the study of amine metabolites from spinal fluid and urine. Clinical studies of vasopressin and oxytocin function are a major current focus. Recent studies have also focused on CRF and endogenous opiate systems, their basic biophysiology, and potential pathologic regulation in affective and endocrine disorders. Clinical and laboratory studies are ongoing in close collaboration with Dr. Lynn Loriaux of the Developmental Endocrinology Branch of the NICHD.

Clinical Neuropharmacology Branch—Dennis L. Murphy, M.D.

This branch conducts clinical and laboratory studies designed to contribute to the understanding of the mechanisms of therapeutic drug effects in individuals with affective disorders, obsessive-compulsive symptoms, dementias, and other behavioral disorders. The studies are primarily based on a 10-bed psychiatric research ward. The inpatient investigations are complemented by an outpatient program with an emphasis on psychobiologic studies of possible high-risk segments of community populations.

Support for the clinical studies includes a behavioral assessment and data processing program, as well as a biochemistry/neuroendocrinology laboratory under the direction of Robert M. Cohen, M.D., Ph.D. Other neurochemical laboratory studies are oriented toward cellular pharmacology using electron microscope approaches (Jonathan Costa, M.D., Ph.D.) and toward neurotransmitter-related enzymes (Dennis L. Murphy, M.D.). Facilities for nonhuman primate studies (directed by Thomas Insel, M.D.) and studies of small animals are also available in the branch.

The ward research investigations, which are balanced between biologic-pharmacologic and psychologic-phenomenologic approaches, take place in the setting of an active milieu treatment program. The incoming medical staff fellow, depending on his or her prior research and clinical experience, will usually participate at first in ongoing research projects and the clinical program. With increased experience, the fellow will work with a senior staff member in the planning, design, and implementation of one or more research projects to be initiated in the first year and completed in the second or possibly third year.

Emphasis is on the strategies and methods used in clinical research and laboratory approaches to clinical problems. Specific research projects range from psychological studies of the characteristics of individuals who do or do not respond to specific drugs and to laboratory or animal studies of the effects of drugs on cellular processes, including enzyme activity, membrane transport, and neurotransmitter receptor functions. Studies of psychoactive drug effects on neurotransmitter metabolism and neuroendocrine function are a particular focus in both the clinical and nonhuman primate areas.

Drugs currently under study include selective monoamine oxidase inhibitors, some natural precursors of brain neurotransmitters, and lithium carbonate, as well as other antidepressants and some new investigational compounds. Special areas of study at present include investigations of adaptational responses to longer-term drug administration in neurotransmitter receptors and secondary effector systems; animal models of affective disorders; neuroendocrine responses, and other characteristics differentiating subgroups of psychiatric patients; studies of monoamine oxidase; the development of new electron microscope-based techniques (e.g., energy loss spectroscopy) for the study of the storage and metabolism of neurotransmitter amines and other substances in cells; and methods for the assessment of behavioral and psychological states.

Clinical Psychobiology Branch—
Thomas A. Wehr, M.D., Acting

Clinical research is conducted in areas related to affective illness (depression and mania) and sleep disorders. Laboratory research involves studies of the neurobiology of sleep and circadian rhythms. Structurally the branch is divided into the Clinical Research Unit, the Unit on Sleep Studies, and the Outpatient and Follow-up Unit. Throughout the 2- to 3-year assignment, the fellow's time is divided among clinical care-ward management, clinical research, and laboratory research, depending on interest. Direct responsibility for research projects is assumed from the beginning.

- Clinical Research Unit—
  Thomas Wehr, M.D.

The unit represents the major research resource of the branch and is located in a 15-bed psychiatric research ward.

The major focus of clinical research on the inpatient unit is the treatment of affective disorders and the investigation of abnormalities in the timing and phase of circadian rhythms in depression, mania, and sleep disorders.

Both pharmacological and nonpharmacological treatment strategies are studied. For example, the effects of antidepressants and thyroid hormone on the cycles of mania and depression are currently being evaluated. Non-pharmacological treatments include sleep deprivation, altering sleep schedules, and manipulation of environmental light. We have the capability of studying similar interventions in normal volunteers and animals. We are evaluating the possible synergistic effects of medications and non-pharmacologic treatments. Neuroendocrine studies involving, for example, the thyroid and adrenal and the effects of light on melatonin secretion are being conducted.

The characteristics of circadian systems in patients and normal volunteers are studied in conditions where they are isolated from all time cues for periods up to 4 weeks. New techniques and instruments make it possible to study continuously changes occurring in motor activity, body temperature and EEG-recorded sleep.

- Outpatient and Follow-up Unit—
  Norman Rosenthal, M.D.

A common theme of both inpatient and outpatient studies is the longitudinal study and treatment of cyclical affective disorders and sleep disorders. Outpatients with affective disorders are followed in the clinic and admitted for psychobiological and treatment studies. We encourage the study and treatment of interesting subgroups. For example, patients who regularly become depressed during certain seasons have been identified and are studied and treated biologically and psychologically.

- Unit on Sleep Studies—
  Wallace Mendelson, M.D.

This unit conducts studies of sleep physiology and pharmacology, with emphasis on the role of sleep in psychiatric illnesses such as depression. Other areas of concern are sleep as a circadian rhythm and primary pathologies of sleep such as sleep apnea syndrome. Psychophysiologic studies of insomnia and hypersomnia are pursued at a clinical level. Animal sleep studies involve experimentation with possible naturally occurring "sleep factors" and the role of benzodiazepine receptors in sleep and anxiety. Electronic analysis of the EEG is done at both clinical and animal levels.

- Laboratory Studies—
  Gerard Groos, Ph.D.

The basic research program of the Clinical Psychobiology Branch focuses on the neuropharmacologic, electrophysiologic, and neuroanatomic mechanisms that underlie circadian rhythmicity in mammals. To this end, we study the physiology of a putative "biological clock" in the brains of rodents: the suprachiasmatic nuclei. These nuclei are investigated at various levels of analysis. Microelectrode recordings are performed *in vitro* and *in vivo* to study the basic mechanisms of rhythm generation. Lesion studies in freely moving animals enable us to further elaborate the anatomic pathways mediating the regulation of the sleep-wake cycle. Microiontopheretic techniques are used to define the role of endogenous transmitters in the generation and synchronization of circadian rhythms.

Clinical Neuroscience Branch—
Steven M. Paul, M.D.

The branch conducts a multidisciplinary program in basic and clinical neuroscience and attempts to integrate data on the biochemistry and pharmacology of the central nervous system with an understanding of the pathogenesis and treatment of major psychiatric diseases. Structurally the Neuroscience Branch consists of four sections: Molecular Pharmacology, Preclinical Studies, Brain Biochemistry, and Clinical Studies. Medical staff fellows are assigned to the clinical research unit, usually for a period of 2 to 3 years. During this time their activities are divided between direct patient care, clinical research, and laboratory research, depending on the interests and talents of the individual. Medical staff fellows will be encouraged to become actively involved in ongoing research projects, as well as to develop their own research protocols as early as possible. Collaborations between individual medical staff fellows and the three basic science sections, on both laboratory and clinical research projects, will also be encouraged. The overall goal of the branch is to create a climate in which sound scientific findings can be applied to an understanding of both normal and abnormal behavior.

- Section on Preclinical Studies—
  Steven M. Paul, M.D.

The major interests of the section concern the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with neuronal membranes, including membrane receptors and ion channels. Wherever possible, basic laboratory studies are applied to behavioral and clinical problems. Several receptor systems are currently under investigation, including receptors for benzodiazepines, tricyclic antidepressants, serotonin, adenosine, and the neuropeptide cholecystokinin. The role and regulation of these systems are investigated by: (1) biochemical and pharmacologic characterization of the recognition sites; (2) isolation and characterization of the endogenous modulators of these sites; (3) development of appropriate *in vitro* models for studying these receptors (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharmacologic experiments in animals; (6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor changes that correlate with the behavioral manifestations of these genetic mutations; and (7) post-receptor events, including alterations in calcium transport and cyclic nucleotide levels.

- Section on Brain Biochemistry—
  Candace B. Pert, Ph.D.

It has recently become apparent that neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell surface receptor. We use radiolabeled ligands with fully preserved biologic activity to study drug and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain where neuroanatomic relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus with emphasis on identifying opiatergic neurocircuitry, systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (e.g. angeldustin, bombesin, substance P, neurotensin, and CCK) are also being studied. In short, the thrust of our laboratory efforts is the characterization, measurement, visualization, and solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally.

- Section on Molecular Pharmacology—
  Steven M. Paul, M.D., Acting

Current investigations are directed toward an understanding of the regulation and actions of receptors at the cellular level. Two examples of current work are studies of: interactions between GABA receptors and benzodiazepine receptors; the synergistic actions of these receptors on neuronal firing and biochemical parameters of cellular activity and benzodiazepine receptor purification; and mechanisms that control the number and functioning of β-adrenergic receptors in cultured cell lines and alterations in β-adrenergic receptors that occur following exposure of cells to β-adrenergic agonists (desensitization).

- Section on Clinical Studies—
  David Pickar, M.D.

This unit encompasses the entire inpatient evaluation and treatment of patients on the clinical research unit. Current research problems include investigations of the clinical phenomenology of schizophrenia and the similarities and differences between schizophrenia and schizoaffective disorders. Studies on the role of central and peripheral opioid systems (i.e., enkephalin, β-endorphin) in stress, schizophrenia, and depression, and inpatients with acute and chronic pain are also ongoing. Laboratory investigations on possible peripheral biologic markers in schizophrenia, as well as various affective disorders (i.e., platelet [^{3}H] imipramine binding, serotonin transport, RBC membrane fluidity), are being carried out in hopes of unraveling vulnerability factors in these disorders.

Other areas of interest involve attempts to delineate vulnerability markers (state-independent and state-related variables); the prediction of antipsychotic drug response and prognosis; exploration of GABA, neuropeptides (such as endorphins and vasopressin), and other neurotransmitter systems for their potential involvement in psychosis; evaluation of new antipsychotic drugs; assessment of pharmacologic and endocrinologic aspects of schizophrenia and schizoaffective illness; immunologic aspects of schizophrenia; study of CAT scan abnormalities; cognitive and psychophysiologic evaluations; and PET scan studies.

Laboratory of Clinical Science—
Irwin J. Kopin, M.D.

This laboratory conducts research on the biochemistry, physiology, and pharmacology of the nervous system and relates these findings to clinical areas in medicine, neurology, psychiatry, and anesthesiology. Applicants for the medical staff fellow program in laboratory research should have at least 1 year of clinical training, whereas those interested in clinical research are required to have at least 2 years of postdoctoral training in neurology or psychiatry before arrival for duty.

The research program objectives are attained through the cooperative efforts as well as the independent research of investigators in the various sections and units of the laboratory.

- Section on Pharmacology—
  Julius Axelrod, Ph.D.

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory examines control mechanisms of the biochemistry of the pineal gland and membranes.

- Section on Histopharmacology—
  David M. Jacobowitz, Ph.D.

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic), and cholinergic and gabaminergic neurons in the brain and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical and neurochemical analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying bases for behavioral changes. The catecholamine histofluorescence method, the study of drugs, stress, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Behavioral studies being pursued involve the genetic fat rat, spontaneous hypertensive rat, sexual and reproductive function and various stress manipulations. Neuronal amines, enzymes, and peptides are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence and radioimmunoassay are also being used to study the localization of enzymes (DβH) and peptides (α-MSH, bombesin, enkephalin, vasopressin, substance P, and pancreatic polypeptide) in the brain. Studies of peptides in human and animal brain and cerebrospinal fluid are currently under way. These are designed to examine the dynamics of release of peptides within the brain.

- Section on Medicine—
  Irwin J. Kopin, M.D.

The research efforts of this group center around the study of biochemical and physiologic effects of drugs and toxins that alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes that control their synthesis in both the central and peripheral sympathetic nervous systems. The techniques used include radioisotopic methods *in vivo* and *in vitro*, tissue slices, perfused organs, and organ and tissue cultures. Brain lesions, direct stimulation of specific areas in the brain, chronic indwelling catheters placed in arteries, veins, or cerebral ventricles are used in studies in animals. Procedures are developed for application to clinical studies for evaluation of neurotransmitter and neuroendocrine function in human subjects. These studies are carried out in cooperation with other clinical units and include various disorders of the autonomic nervous system (orthostatic hypotension, hypertension, familial dysautonomia), neuropsychiatric disorders (Korasakoff's syndrome, Huntington's disease), as well as the major psychoses. Plasma, urine, and CSF are analyzed for various drugs, amines, and metabolites, and the rates of utilization or synthesis determined using radioimmunologic, enzymatic, or mass spectroscopic techniques.

- Section on Analytical Biochemistry—
  Sanford P. Markey, Ph.D.

The unit develops techniques for clinical studies of neurotransmitters, neurohormones, peptides and their metabolites, and drugs that influence their formation or disposition. Projects include the synthesis of stable isotope-labeled analogs of amines and metabolites for human kinetic studies, the isolation and quantitative assay of compounds of interest, and the design and construction of alternate ion sources for mass spectrometry. Current projects include the synthesis of ^{18}O-dopamine as a probe of peripheral norepinephrine metabolism in humans; the negative ion mass spectral quantitation of levels of melatonin in plasma and its alteration by disease and pharmacologic intervention; and the assay of the major urinary melatonin metabolite for developmental studies in neonates, infants, children, and in patients with disorders of the sympathetic nervous system or who receive drugs influencing the sympathetic nervous system.

- Section on Clinical Pharmacology—
  William Z. Potter, M.D., Acting

The central focus is the study of the mechanisms of action of antidepressants and other psychoactive drugs using integrated biochemical and pharmacokinetic studies in man and animals. At present, clinical studies involve both patients with affective illness and normal volunteers. New biochemically specific drugs are examined to identify common biochemical effects using measures in cerebrospinal fluid, plasma, and urine. Parallel investigations are done in animals in which more invasive and detailed studies of CNS biochemical alterations are possible. Since the noradrenergic and serotonergic systems can be directly or indirectly implicated in the action of all known antidepressants, the pretreatment noradrenergic and serotonergic "tone" of patients with affective illness is contrasted to that in volunteers and those with other psychiatric illnesses. Techniques include assay of antidepressants, hormones, neurotransmitters, and their metabolites in tissues and body fluids by radioimmunoassay, HPLC, or GC-MS; pharmacokinetic modeling of data in neurotransmitter systems; *in vitro* binding techniques for studying neurotransmitter receptor alterations; and the development of appropriate animal models.

- Section on Experimental Therapeutics—
  Michael H. Ebert, M.D.

The section conducts studies of the clinical pharmacology of a variety of neuropharmacologic agents, including clonidine and phencycliding. Neurochemical, neuroendocrine, and pharmacokinetic experiments and drug trials are in progress in a variety of neuropsychiatric and psychosomatic syndromes. The section operates a clinical research unit to pursue these studies. In collaboration with other investigators in the Laboratory of Clinical Science, experiments are in progress in primates and man to measure turnover rates of brain monoamines by stable isotape labeling techniques and changes in synthesis rates produced by disease states and/or pharmacologic treatment. Diseases of interest at the present time include orthostatic hypotension, anorexia nervosa, bulimia, several presenile dementias, and hyperactivity in children.

- Section on Childhood Mental Illness—
  J. L. Rapoport, M.D.

This unit operates on a four-bed day and/or overnight hospitalization inpatient program in collaboration with the Section on experimental Therapeutics, Laboratory of Clinical Science, and independently on a pediatric ward maintained by NICHD. Current focus is on diagnostic assessment and drug treatment of hyperactive children. Drug studies include pharmacokinetic studies of drugs given to children and studies of kinetics and metabolism of neurotransmitter systems via body fluids.

Also under way are outpatient studies of obsessive-compulsive children, and the evaluation of children whose parents have been hospitalized here in the past for affective illness and offspring of alcoholics.

Laboratory of Cell Biology—
Michael J. Brownstein, M.D., Ph.D.

The members of this group have a variety of research interests. These include light and electron microscope-level neuroanatomy, chronobiology, developmental neurobiology, biosynthesis of biologically active molecules, isolation of novel peptide hormones, and regulation of intracellular processes by chemical messengers.

Laboratory of Developmental Psychology—
Marian Radke-Yarrow, Ph.D.

This program conducts research on the behavioral development of children, primarily affective and social development, and on interrelations between stressful conditions—biomedical or psychosocial—and the functioning of children. There is an emphasis on research strategies and methods in the investigation of child behavior. Variables such as mood, aggression, altruism, and social cognition are of special interest. Laboratory studies, as well as field studies, are conducted on children, infants through adolescents. Much of the research is collaborative, involving investigators in other laboratories of NIMH and other institutes. Specific projects include studies of early problem aggression, developmental continuity and discontinuity in affective and social characteristics of children, effectiveness of various therapies for different types of problem behavior in children, and child rearing environments and their consequences for children. Among the risk groups being studied are children reared by parents with affective disorders. Biomedical conditions studied in relation to behavior include normal developmental changes in adolescence, hormonal abnormalities, and severe physical disease states.

Laboratory of Psychology and Psychopathology—
Allan F. Mirsky, Ph.D.

This laboratory conducts a broad program of basic and clinical research on attention, learning, and memory in both humans and monkeys and on the neurophysiologic and psychophysiologic mechanisms involved in these processes.

Studies on the neurophysiology of attention in monkeys with a single unit recording from various parts of the brain and with stimulation and ablation techniques are focused on the investigation of animal models of cognitive processes that may be impaired in many human psychiatric and neurologic disorders. Parallel studies of congitive processes in psychiatric and neurologic patients and in normal controls using similar behavioral techniques are designed to permit direct comparison with the animal work.

Studies of memory functioning in a wide variety of patients and of pharmacologic influences on memory in humans are being conducted by Herbert Weingartner, Ph.D. Studies of attention and autonomic nervous system functioning in schizophrenics and in other patients and drug effects on these processes are being done by Theodore P. Zahn, Ph.D. Investigations of attention and cortical and brainstem averaged evoked potentials in psychiatric and neurologic patients are under way.

Laboratory of Neurobiology
Ichiji Tasaki, M.D.

Current research projects include electrophysiologic, biomechanical, and biochemical studies of the mechanism of excitation of nerve cells and fibers. We are using extremely sensitive mechanical devices constructed in the Laboratory of Neurobiology to analyze mechanical changes associated with action potentials in nerves. These changes are intepreted in terms of structural changes in the axolemma-ectoplasm complex of nerve.

Another major project in this laboratory involves a developmental study of the appearance of excitability in nerve and muscle cells grown in culture. This project involves studies of excitability at three levels of cellular organization: binding studies using a variety of toxins known to affect excitability, studies involving the uptake of sodium by the cells in response to a variety of drugs and toxins, and electrophysiologic responses of the cells to various drugs and toxins. The goal of this work is to understand how these cells become excitable and, thus, the biochemical mechanism of excitability.

Laboratory of General and Comparative Biochemistry—
Giulio L. Cantoni, M.D.

Investigations are concerned with the mechanisms and pathways of biological methylation, alkaloid biosynthesis, opioid peptides, cellular differentiation, and gene expression in eukaryotes. The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, mechanism of drug addiction, muscle differentiation in cell culture, and genetic engineering.

- Section of Alkaloid Biosynthesis—
  S. Harvy Mudd, M.D.

This section studies the enzymes involved in biosynthesis in methylation in plants and their control. The section also studies enzymatic mechansims of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

Laboratory of Cerebral Metabolism—
Louis Sokoloff, M.D.

- Section on Developmental Neurochemistry—
  Louis Sokoloff, M.D.

A broad program of investigation is conducted on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds such as hormones that play important physiologic roles in CNS function. A method recently developed in this laboratory permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic, pharmacologic, and pathologic states.

Laboratory of Neurochemistry—
Seymour Kaufman, Ph.D.

The following areas are studied: the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine-hydroxylating system. In addition to studies with the pure enzymes, emphasis is placed on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia. This laboratory investigates the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin, the relationship between the properties of the enzymes, and physiologic regulation of rates of synthesis of these neurotransmitters; the biochemical basis for skeletal muscle hypertrophy, including the effects of exercise and neural factors in the process; cell-surface membrane proteins and receptors in their role in cellular differentiation; and the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

Laboratory of Neurophysiology—
Edward V. Evarts, M.D.

This laboratory combines the techniques of electrophysiology, neuroanatomy, neurotransmitter receptor localization, and experimental psychology in studies aimed at understanding the brain circuits, cell types, and receptor mechanisms relevant to neuropsychiatric illness. Research is organized in four units.

- Unit on Motor Systems—
  Edward V. Evarts, M.D.

This unit is engaged in studies of single nerve cell activity in basal ganglia, cerebellum, thalamus, and motor cortex of monkeys performing learned movements. The aim of the work is to achieve an understanding of the way in which the activity of these structures is integrated during normal movement and how diseases within these structures impair movement.

- Unit on Dynamic Brain Structure—
  Miles Herkenham, Ph.D.

Traditional neuroanatomical techniques reveal features of static morphology; however, the use of fresh brain cut into sections in the cryostat enables studies of the localization of neurotransmitter and drug receptors, enzymes, 2-deoxyglucose metabolism, and architecture. This unit is engaged in studies of correlative, comparative, and developmental features of opiate receptor localization revealed by autoradiography. Related neurochemical and metabolic markers are visualized to show the interaction of the opiate system with other brain systems during normal development and function, after experimental manipulation or in cases of disease-induced abnormalities.

- Unit on Motor Psychophysics—
  Jerome N. Sanes, Ph.D.

The work in this unit is aimed at applying the principles of motor psychophysics to an understanding of the pathophysiology of clinical disorders including Parkinson's disease, peripheral neuropathy, cerebellar ataxia, tardive dyskinesia, and other conditions with prominent motor impairments. The aim of the work is to obtain more reliable and objective measures for evaluation of long-term efficacy of therapeutic agents as well as to provide information on the basic neural mechanisms relating brain lesions to altered motor behavior. There are close collaborative relations with clinical branches in several different institutes.

- Unit on Cerebral Cortex—
  Steven P. Wise, Ph.D.

Work in this unit combines techniques of basic neurobiology with techniques of single cell recording in operantly conditioned rats and monkeys. The aim of the work is to discover how the different topographic divisions of the sensorimotor cortex interact in behaving organisms. Special attention is devoted to the different sorts of sensory information that are processed in different subdivisions of the sensorimotor cortex and to how behavioral set and intention for future action are reflected in regions such as the premotor and supplementary motor areas of the cerebral cortex. Specialized neurobiologic techniques (e.g., intracellular injection of neuronal markers and laminar elctrophysiologic analysis) are carried out in parallel with the behavioral studies.

Laboratory of Brain Evolution and Behavior—
Paul D. MacLean, M.D.

Opportunities are offered for research on evolutionary, developmental, ethologic, and ecologic factors relating to brain function and behavior. Large outdoor and indoor habitats are available for comparative studies on reptiles, birds, and mammals living under seminatural conditions. The laboratories are equipped for neuroanatomic research, microelectrode recording, brain stimulation, and psychologic testing and have a computer system with high-speed graphics capability for the recording and processing of electrophysiologic and behavior data. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted, species-typical behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior.

Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, ethology, psychology, ecology, paleobiology, and systematics. The laboratory is located at the NIH Animal Center near Poolesville, MD.

Division of Special Mental Health Research—
Richard J. Wyatt, M.D.

This division, located at Saint Elizabeths Hospital, conducts a program of intramural research on special mental health problems, such as psychopharmacology, neuropharmacology, neuroanatomy, sleep, memory, normal and abnormal human behavior, and geriatric psychiatry. Clinical evaluations, treatment, and followup are an integral part of all research protocols.

Adult Psychiatry Branch—
Richard J. Wyatt, M.D.

This clinical research laboratory capitalizes on many discplines in its effort to understand and treat schizophrenia, the psychiatric problems of the elderly, central nervous system regeneration, memory, sleep, and its disorders. The laboratory is set up so that small groups of young scientists may employ biochemical, structural, anatomic, pharmacologic, physiologic, and psychologic techniques in their work with these basic science and clinical problems.

The major focus of the branch's research takes place on three inpatient research wards. Llewellen B. Bigelow, M.D., is the clinical director. There is substantial opportunity to examine drug-free patients and to use pharmacologic probes to discern different patient groups. Three 12-bed research wards housed in the William A. White Building are devoted to schizophrenia research. There is also an outpatient department for studying geriatric psychiatry and schizophrenia and a day hospital. In addition, many of the 1,800 inpatients at Saint Elizabeths Hospital participate in research programs.

- Group on Mass Spectrometry—
  Farouk Karoum, Ph.D.

The laboratory operates two quadruple mass spectrometers which are primarily used in clinical studies to measure neurotransmitters and their metabolites. A major current interest is measuring phenylethylamine (PEA), and endogenous amphetamine-like compound which has been suggested to be elevated in the urine of some paranoid schizophrenic patients.

- Enzymology and Cell Sorting Group—
  Bruce Phelps, Ph.D.

This group is principally interested in evaluating the significance of decreased activities of the enzymes monoamine oxidase and dopamine-beta-hydroxylase, both of which have been reported to be altered in some schizophrenic patients. Clinical data and biological samples from patients and their relatives are routinely analyzed with the aim of understanding the significance of deficits in these enzymes. In addition, the group has a fluorescence-activated cell sorter (FACS III) being used to examine structural differences in various cellular samples (particularly lymphocytes) from schizophrenic patients. Subtle differences in immune systems of these patients are being systematically studied using the FACS. Other cell types are being sorted on the basis of differential binding of fluorescent compounds for further use in tissue culture and animal experiments.

- Section on Aging
  Peter Bridge, M.D., David Shore, Ph.D., and Dilip Jeste, M.D.

This group is actively carrying out clinical studies in geriatric patients with psychiatric illnesses. These include depression, alcoholism, Alzheimer's disease, and tardive dyskinesia. Current studies in depression are attempting to look at pharmacokinetics and to evaluate psychotherapy versus tricyclic antidepressants in a geriatric population. Alcohol studies are being carried out in conjunction with scientists in the Alcohol Institute, in an attempt to understand psychologic and physiologic changes that occur with chronic drug abuse in older individuals. A principal hypothesis about the etiology of Alzheimer's disease is that aluminum deposits accumulate on the DNA of the brains of patients with Alzheimer's disease. This group is currently carrying out a project to determine whether or not decreasing aluminum in the body of patients with Alzheimer's disease has any effect on the course of this illness. Tardive dyskinesia is a principal and serious side effect of the clinical use of neuroleptic drugs. It is far more common in older patients than younger ones. This group is currently trying to determine both the etiology and how we can best prevent tardive dyskinesia in patients who must be on these drugs for long periods of time.

- Basic Neurosciences Section—
  William J. Freed, M.D., and
  Luis de Medinaceli, M.D

This group emphasizes the exploitation of brain grafting techniques to correct lesion-induced behavioral deficits. Currently under study are the characteristics of the brain as a site of transplantation and the potential of brain grafts to effect functional reconstitution. A major success has been in grafting adrenal medulla or substantia nigra to the caudate nucleus, thereby correcting the rotational behavior that develops following unilateral substantia nigra lesions. Destruction of the substantia nigra has been considered by many to be an animal model of Parkinson's disease, and this group is applying these techniques to rats and monkeys in order to develop brain grafting within this model. Other related interests involve the transplantation of endocrine tissue and retinae to the rat brain.

Although fiber sprouting is always observed following peripheral nerve injury, the functional consequences of such injury are variable, and in mammals, functional recovery is frequently slow and incomplete. This group is interested in developing new approaches to peripheral nerve repair, in order to improve the rate and degree of functional recuperation, and to better understand the mechanisms involved in promotion and obstruction of peripheral nerve regeneration in mammals.

- Neuropsychiatry Section—
  Daniel R. Weinberger, M.D., and
  Janice R. Stevens, M.D.

This group is investigating the relationship of behavior and psychopathology to neuroanatomic and neurochemical alterations in the brains of patients with neuropsychiatric disorders, principally schizophrenia. In living subjects, the emphasis in on linking brain structure, metabolism, and function to develop more meaningful dimensions of psychiatric syndromes. Powerful new techniques that are currently utilized include computed tomography (CT), xenon-133 regional cerebral blood flow, and positron emission tomography (PET).

- Section on Schizophrenia—
  Joel E. Kleinman, M.D.

A large human brain bank is the focus of postmortem studies that are evaluating neurochemical, immunologic, and virologic hypotheses of neuropsychiatric illness. Current projects include qualitative and quantitative neuroanatomy, immunocytochemistry. and studies of biogenic amine, peptide, and receptor neurochemistry.

Laboratory of Preclincal Pharmacology—
Erminio Costa, M.D.

Scientific efforts of this laboratory are directed toward the elucidation of neuronal control mechanisms that mediate responses of drugs affecting neuronal function. The laboratory is organized into one group and four sections.

- Group on High-Pressure Liquid
  Chromatography—James Meek, Ph.D.

New methods are developed to investigate drug effects on renovation rates of brain stores of monoamines and neuropeptides.

- Section on Molecular
  Pharmacodynamics—
  Darwin Cheney, Ph.D.

Pharmacologic studies are conducted on the dynamics of acetylcholine in discrete brain nuclei using pulses of deuterated precursors and mass fragmentography, the dynamics of GABA in discrete brain nuclei using pulse labeling with ^{13}C-glucose and mass fragmentography, and the regulation of the dynamics of acetylcholine and GABA by various endogenous neuropeptides.

- Section on Biochemical
  Pharmacology—Norton Neff, Ph.D.

This section conducts investigations directed at the identification of control mechanisms for enzymes that regulate the dynamics of putative brain neurotransmitters and the determination of drug actions on the regulation of turnover rate of brain monoamines using mass fragmentography.

- Section on Neuroendocrinology—
  Alessandro Guidotti, M.D.

Efforts are directed towards the study of: (1) the hypothalamic control of pituitary function, and (2) the modulation by opiate peptides of chromaffin cell response to splanchnic nerve stimulation. The mechanism of action of benzodiazepines and the role of GABAergic mechanisms in the neurobiology of anxiety are also a main research focus of this section.

- Section on Molecular Neurobiology—
  Erminio Costa, M.D.

Investigations are conducted on the regulation of nerve growth factor production by glial cells; the role of chromatin phosphorylation in the regulation of gene expression; the pharmacology of binding of putative neurotransmitters to postsynaptic receptors; the regulation of storage, release, and synthesis of peptides that function as putative neurotransmitters (enkephalins, substance P, angiotensin, and neurotensin); and the identity and kinetic properties of enzymes that regulate the synthesis and metabolism of neuropeptides.

National Institute of Neurological and Communicative Disorders and Stroke

Murray Goldstein, D.O., M.P.H.,
Director
Thomas N. Chase, M.D.,
Director, Intramural Program
Richard L. Irwin, Ph.D.
Laboratory Director
Paul L. Kornblith, M.D.,
Acting Clinical Director

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) provides broad opportunities for post-doctoral training in the basic and clinical neurosciences. Laboratories and clinics operated by the Institute are located principally on the main NIH campus in Bethesda, Maryland. Limited training opportunities also exist at NINCDS facilities in Frederick, Maryland, Woods Hold, Massachusetts, and on Guam. Most medical staff fellows participate in clinical neurosciences research in Institute laboratories and clinics, and have responsibility for the care of patients admitted for study. Some fellows primarily engage in basic laboratory investigations. All work is conducted under the preceptorship of a senior staff member and fellows are encouraged to avail themselves of an active program of teaching seminars, invited lectureships, and ward rounds.

Appointments in Clinical Research

Medical staff fellow positions for the National Institute of Neurological and Communicative Disorders and Strokes (NINCDS) are available in medical and surgical neurology, experimental therapeutics, infectious diseases, neuroimmunology, neuroepidemiology, and developmental and metabolic neurology. Fellows are usually appointed for 2 years, with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on NINCDS wards, involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NINCDS research emphases.

Candidates requiring further information about NINCDS clinical positions for medical staff fellows should write to Thomas N. Chase, M.D., Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 36, Room 5A05, National Institutes of Health, Bethesda, Maryland 20205.

Appointments in Laboratory Research

NINCDS medical staff fellow positions are available in neuro-chemistry, neurophysiology, neuropathology, neurootolaryngology, biophysics, molecular biology, biology, molecular genetics, and other areas of fundamental neurosciences investigation. Appointments are for 2 years, with the possibility of extended affiliation.

Areas of study are developed by each fellow in conjunction with a preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned. Independence and originality of approach are encouraged.

Medical staff fellows have the opportunity to work closely with a large and diverse group of senior investigators, to participate in on-site courses and conferences, and to employ advanced neuroscience technology in the conduct of their research.

For further information on the NINCDS Medical Staff Fellowship Program, write to Thomas N. Chase, M.D., Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 36, Room 5A05, National Institutes of Health, Bethesda, Maryland 20205.

Medical Staff Fellows in Epidemiology

Intramural Research Program—
Thomas N. Chase, M.D.

- Section on Neuroepidemiology—
  Bruce S. Schoenberg, M.D., Dr.P.H., and Roswell Eldridge, M.D.

The section conducts national and interational studies concerning the patterns of neurologic disorders in human populations. Both environmental and genetic factors in disease etiology are considered. The medical staff fellow receives training in the utilization of neuroepidemiologic and neurogenetic techniques to the solution of practical problems in clinical neurology and neurosurgery. Although the section's program involves the application of epidemiologic methods to the study of any disorder of the nervous system, current research concentrates on cerebrovascular disease, brain tumors (including neurogibromatosis), dementia, cerebral palsy, torsion dystonias, multiple sclerosis, parkinsonism, and racial differentials in the occurrence of neurologic disease.

Clinical Branches

Clinical Neurosciences Branch—
Paul Fedio, Ph.D., Acting

Various clinical and electroencephalographic (EEG) aspects of seizure disorders are investigated, with emphasis on diagnosis and localization. Cerebral evoked response techniques are also applied for clinical and research studies. Consultative EEG and cerebral evoked response examinations are provided to neurologic and psychiatric patients within the NIH. Basic investigations are focused on pathophysiologic and pharmacologic aspects, utilizing a kindling model of epilepsy. The appointment of medical staff fellows is for 2 years, and preference is given to applicants with experience in clinical neurology and electrophysiology.

Developmental and Metabolic Neurology Branch—
Roscoe O. Brady, M.D.

- Section on Enzymology and Genetics—
  Roscoe O. Brady, M.D.

Principal research efforts concern the pathologic biochemistry, diagnosis, carrier identification, and genetic counseling related to inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, Krabbe's disease, and Tay-Sachs disease, along with the development of enzyme purification procedures for replacement therapy trials. Other studies include alterations of complex lipid metabolism in neoplastic cells and the role of trophic hormones with cell membrane receptors.

- Section on Neurochemical Methodology—
  Andrew E. Gal, Ph.D.

This section is involved in the preparation of widely useful substrates for the facile diagnosis of metabolic disorders, the development of ultramicroanalytic procedures for monitoring the effects of enzyme replacement therapy, and the synthesis of novel lipids and lipid analogs for metabolic studies in normal and pathologic tissues.

- Section on Myelin and Brain Development—
  Richard H. Quarles, Ph.D.

Research is primarily concerned with

the composition and metabolism of myelin components in the developing nervous system and an examination of abnormalities of their structure and function in demyelinating conditions such as multiple sclerosis.

- Section on Physiology and Metabolism—
  Roscoe O. Brady, M.D., Acting

Principal research involves the delineation of the molecular basis of nerve excitation as related to structural and functional sidedness of natural and artificial membranes.

- Section on Membrane Biochemistry—
  Peter H. Fishman, Ph.D.

Research is directed towards the biosynthesis, organization, and function of cell membranes including transmembrane signaling of receptor-mediated information, regulation of membrane enzymes, biogenesis of membrane components, and topologic organization of cell-surface receptors.

- Section on Clinical Investigations and Therapeutics—
  John A. Barranger, M.D., Ph.D.

Investigations are concerned with heritable and acquired disorders of metabolism, with emphasis on the elucidation of pathogenetic mechanisms and the development of measures for the treatment of these conditions including replacement of enzymes in deficiency disorders.

Experimental Therapeutics Branch—
Thomas N. Chase, M.D., Acting

- Section on Pharmacology—
  Thomas N. Chase, M.D.

This section conducts an integrated program of preclinical and clinical studies directed towards the rational development of improved therapies for extrapyramidal and dementing disorders. Current investigations focus on the pharmacology of central transmitter systems; biochemical and cerebral imaging (positron emission tomography) approaches are used to related neurologic symptoms to dysfunction of special classical or peptidergic systems. Pharmaceutical testing is carried out in animal models and in research patients.

- Section on Clinical Epilepsy—
  Roger J. Porter, M.D.

The major effort of this section is the intensive monitoring of patients with uncontrolled seizures by videotape recordings and telemetered electroencephalography, the study of the metabolism and efficacy of various antiepileptic agents, and studies on the usefulness of new scanning procedures, such as positron emission tomography.

- Section on Biochemical Neuropharmacology—John Kebabian, Ph.D.

Research is conducted on the biochemical properties of synaptic receptor mechanisms in the central nervous system (CNS) and drug-induced modification of receptor activity.

- Section on Physiological Neuropharmacology—
  Judith Walters, Ph.D.

Measurements are undertaken to evaluate the effects of drugs on the electrical discharges of single nerve cells in various regions of the CNS.

- Unit on Neuroendocrinology—
  Thomas O'Donohue, Ph.D.

The unit conducts preclinical investigations of neurotransmitter biochemistry which will eventually lead toward a better understanding of neurological disease and the development of new pharmacological therapeutic agents. Particular emphasis is placed on the identification of important neuropeptide systems in the central nervous system. Studies focus on anatomy, biosynthetic processes, receptors, and physiological action of these new neurotransmitter systems.

Infectious Diseases Branch—
John Sever, M.D., Ph.D.

- Section on Immunochemistry and Clinical Investigations—
  Sidney Houff, M.D.

The pathogenesis of multiple sclerosis, Epstein-Barr virus infections, amyotrophic lateral sclerosis, and progressive multifocal leukoencephalopathy is under study. Persistent perinatal infections are also being investigated. The role of viruses and cellular immune responses in patients and experimental animals is being tested. Clinical work is done on abnormal antibody and cellular immune reactions in these patients.

- Marinos C. Dalakas, M.D.

The immune and viral pathogenesis of neuromuscular disorders is being investigated and clinical therapeutic trials are conducted. The role of viruses and immune responses in patients with Guillain-Barré syndrome, chronic relapsing polyneuropathies, polymyositis/dermatomyositis, post-poliomyelitis, ALS, and Reye's syndrome is being studied. The mechanism of amyloid deposits and the specific immune nature of paraproteinemia is being investigated in patients with amyloid and paraproteinemic polyneuropathies. Studies are also conducted in patients with amyotrophic lateral sclerosis (ALS) using the PET scan to investigate changes in the cerebral metabolic rate for glucose in the motor cortex, and experimental therapeutics trials with new immunomodulating agents are explored. Clinical research in these areas is combined with muscle and nerve biopsy techniques, muscle histochemistry, immunocytochemistry, and characterization of function and markers of lymphocyte subsets.

- Section on Neurovirology—
  Maneth Gravell, Ph.D.

This section is involved in research on viruses as causes of tumors of the brain, PML, MS, Reye's syndrome, and cerebellar disease with infectious mononucleosis (Epstein-Barr virus), as well as experimental models of persistent virus infections. Methods include tissue culture, cocultivation, new tests for cellular immunity, and antibody determinations.

- Section on Experimental Pathology—
  W. T. London, D.V.M.

Studies of perinatal infections that cause birth defects and persistent central nervous system infections are conducted in monkeys and small laboratory animals. Papovaviruses, cytomegaloviruses, toxoplasmosis, and herpes viruses are being used. Methods for direction, treatment, and prevention are being developed. Persistent infections with polyomaviruses, progressive multifocal leukoencephalopathy, and glioblastomas are under investigation.

One medical staff fellow is appointed annually for 2 years. This individual participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as fellows for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Surgical Neurology Branch—
Paul L. Kornblith, M.D.

This branch investigates and treats clinical problems of disordered neuronal and glial proliferation and differentiation. A major part of the program is devoted to the study of intracranial tumors including pituitary tumors. Problems of both central and peripheral neuronal and glial regeneration are also under study. Clinical research in these areas is combined with basic techniques of cell biology, tissue culture, biochemistry, immunology, pharmacology, and light and electron-microscopic histology to provide for an in-depth exploration and, ultimately, new approaches to these problems.

The mechanism of pain sensation is currently investigated in the neurophysiology laboratory. The responses of the nerve cells at different levels in the CNS are recorded in animals with extracellular or intracellular microelectrodes and pharmacologic agents are applied through micropipettes.

Experimental neuropathology and neuroimmunology is emphasized in a program which includes clinical diagnostic neuropathology. Biochemistry, morphology, and immunochemistry of neoplasms are studied as means of improving detection and treatment and as clonal models of their nonneoplastic counterparts in nervous and lymphoid tissues.

Studies are being carried out on cell-mediated immune mechanisms in human brain tumor patients, including delineation of the effectiveness of various forms of cell-mediated immunity to contribute to the destruction of brain tumors, examination of the ability of brain tumors to elicit cellular immune responses both *in vivo* and in model systems *in vitro,* and exploration of possible modes of altering brain tumor cells so as to increase their immunogenicity. This work is complemented by studies in animal models on basic mechanisms of cell-mediated immune lysis of tumor cells.

The medical staff fellow participates in the care of patients on the various protocols of the Surgical Neurology Branch as well as consultative care of patients with neurosurgical problems in all the NIH institutes. The fellow receives training in the diagnostic and operative techniques of surgical neurology with special emphasis on microneurosurgery both in the animal laboratory and in the operating room. In addition, there will be opportunity for work in the laboratory with training in a wide range of cell biology techniques, with special emphasis on tissue culture, immunoneurology, and electron microscopy. Experimental surgery and other therapy in animal models as it relates to the clinical problems under study will also be performed. The fellow also works in collaboration with senior scientists or independently in specific laboratory areas as his or her experience and interest dictates.

- Section on Neuroradiology and Computed Tomography—
  Giovanni Di Chiro, M.D.

Work in this section currently focuses on the latest applications of transmission computed tomography and its further development as a noninvasive method for morphologic and functional studies of the nervous system. The section is also very actively involved in emission computed tomography using positron emitting radionuclides (positron emission tomography). Particular emphasis is placed on correlative studies between transmission and emission-computed tomography.

Neuroimmunology Branch—
Dale E. McFarlin, M.D.

Research is performed in the following areas: characterization of the immune response to viral agents, such as measles which causes chronic infection in patients with neurologic diseases; study of certain animal models; study of model autoimmune diseases such as experimental allergic encephalomyelitis; assessment of the immune response to components of membranes in the peripheral nervous system and CNS; evaluation of immune function in patients with chronic neurologic disorders of unknown etiology, such as multiple sclerosis and parkinsonism, which may be related to either a persistent infection of the nervous system or immunopathologic mechanisms; assessment of the immune reactivity in human diseases believed to have an autoimmune etiology such as myasthenia gravis; and assessment of new therapeutic agents which alter the immune response.

Two medical staff fellows are appointed annually for 2 years. These individuals participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as research associates for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Basic Research Laboratories

Laboratory of Central Nervous System Studies—
D. Carleton Gajdusek, M.D.

This laboratory is engaged in two studies: (1) The medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior, and learning. High incidence and other unusual foci of chronic CNS diseases, asthma, parasitic and viral diseases, congenital metabolic defects, atypical patterns of puberty and aging, toxic and deficiency syndromes, and unusual behavior syndromes, where isolation or cultural stereotypy may contribute to epidemiologic solutions, are under study. Aspects of learning and socialization in primitive disappearing cultures are documented using still and cinema photography and sound recording. New methods of handling such data for research are developed. (2) The slow, latent, and temperate virus infections, with particular attention to chronic degenerative neurologic disease and basic virologic and immunologic studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by unconventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie, and mink encephalopathy) that form a new group of microorganisms tentatively called "viruses," although they contain much smaller genetic information and possess very different properties than any other group of viral agents. The biological and molecular characterization of these unconventional viruses is the major focus of the work. Aging of the brain, Alzheimer's, Pick's, Parkinson's, and Huntington's diseases, multiple sclerosis, amyotrophic lateral sclerosis, chronic epilepsies, and other diseases are intensively studied in microbiological, immunologic, genetic, and biochemical laboratories and clinics and in foci of high incidence throughout the world.

Laboratory of Molecular Genetics—
Robert A. Lazzarini, Ph.D.

This laboratory investigates the component molecular events that participate in the replication and expression of the genetic materials of mammalian cells and their viruses. Genetic, biochemical, and recombinant DNA techniques are employed in the study of the replication and transcription of genes that ultimately lead to their expression as protein. These studies are directed toward a full understanding of the delicate interplay between the complementing genetic elements in normal cells, chimeric cells, and cells persistently infected with viruses.

- Molecular Virology Section—
  Robert A. Lazzarini, Ph.D.

This section studies aspects of virus-host interactions at the molecular level. These include viral penetration of host cells, viral replication, and the assembly of progeny particles. Particular attention is focused on the involvement of host factors in the replication of the viral genome and the relationship of these to viral host range, persistency, latency, and cytopathology.

- Recombinant Genetics Section—
  Robert A. Lazzarini, Ph.D.

Studies are under way of eukaryotic gene expression and genetic complementation in cultured mammalian cells. These studies employ both recombinant DNA and classical biochemical techniques to probe the control of gene transcription, the processing of primary transcripts, and eventual expression of these RNA's as proteins.

- Neural and Molecular Ultrastructure Section—
  Monique Dubois-Dalcq, M.D.

Studies are under way on: (1) growth factors and purification methods of rodent and human nerve cells, and (2) how nerve cells are affected by neurotropic viruses. More specifically, virus tropism and assembly is studied in nerve cells as well as susceptible cells. Methods employed consist of immunolabeling for light and electron microscopy as well as microinjection of monoclonal antibodies to viral proteins into living cells. (3) The emergence and assembly of myelin proteins during nervous system development using immunocytochemical methods are examined. Similar methods are used to study the alternations in myelin proteins in diseased nerve.

Laboratory of Neural Control—
Robert E. Burke, M.D.

Fundamental research is conducted on the properties of mammalian nerve cells and on the organization of the mammalian CNS with particular reference to studies of the control of movement. Current experimental studies involve three main areas: 1) the CNS control of spinal cord motoneurons and in turn the control exerted by these cells on the muscle fibers innervated by them, 2) the organization of information-processing systems in the spinal cord, and 3) the activity of motor cortex neurons and of individual peripheral afferents during normal movement in intact animals. Such studies utilize established as well as newly developed techniques for electrophysiologic recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The laboratory has facilities for the development of specialized experimental equipment and novel electrode designs suitable for chronic implantation, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

Laboratory of Neurochemistry—
Janet V. Passonneau, Ph.D.

Research is conducted on molecular events that underlie the normal functioning of the nervous system and derangements that occur in neurologic diseases.

- Section on Cellular Neurochemistry—
  Janet V. Passonneau, Ph.D.

Section is involved in studies on metabolism in neural tissues. Emphasis is placed on the microanalytical techniques used to measure metabolites in discrete regions of the brain or in single cells. Projects include the metabolic response of retinal layers to light and dark adaptation, the regional alterations of energy metabolites in ischemia, the role of guanine nucleotides in brain function, and glycogen metabolism in tumor cells of neural origin.

- Section on Enzyme Chemistry—
  Wayne Albers, Ph.D.

The enzymatic mechanism of active Na+ and K+ transport is investigated. Other current projects involve g-aminobutyric acid metabolism, brain mitochondria, and membrane receptors.

- Section on Neurochemical
  Pharmacology—W. David Lust, Ph.D.

The section is interested in the role of energy metabolism and of cyclic nucleotides in brain during and after an ischemic episode and in the various stages of experimentally induced seizures *in vivo.* Molecular mechanisms involved in these neurologic disorders are examined in *in vitro* models. Other projects include studies on anticonvulsants and other neurotropic agents.

- Section on Neuronal Development
  and Regeneration—
  Andrew Zalewski, M.D.

This section is attempting to elucidate the factors involved in nerve fiber regeneration, trophic nerve function, and selectivity and plasticity in the formation of neural connections. A variety of neurohistologic, histochemical transplantation, and immunologic techniques are being used in these studies.

Laboratory of Neuro-Otolaryngology—
Jorgen Fex, M.D., Ph.D.

Inner ear neuronal mechanisms are being studied in mammals. The long-range purpose of the project is to study the biochemistry, morphology, pharmacology, and physiology of inner ear neurons and cells and their interactions and to describe the mechanisms of these interactions. A second project concerns the synaptic transmission and neuronal connections of the mammalian cochlear nucleus. A multidisciplinary approach is being used for this project. A major, long-term program of this laboratory is to solve problems concerning hereditary deafness in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models.

Laboratory of Neuropathology and Neuroanatomical Sciences—
Igor Klatzo, M.D.

The laboratory recognizes the scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomic sciences. Thus, investigations on mechanisms operative in various neuropathologic conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system.

- Section on Cerebrovascular
  Pathology—Igor Klatzo, M.D.

Research is conducted on various aspects of pathophysiology of cerebral ischemia and brain edema. Elucidation of the pathomechanisms involved is attempted by evaluation and correlation of various parameters, such as changes in blood flow, electrical impedance, water content, electrolytes, glucose metabolism, behavior of the blood-brain barrier, and morphological alterations in various models of ischemia and traumatic brain injury.

- Section on Neurocytobiology—Maria Spatz, M.D.

This section investigates the normal and pathological properties of cerebral endothelium which is the main substrate of the blood-brain barrier. The investigations include observations on transport mechanisms in endothelial cells, on their receptors, and on the effect of various substances in modifying barrier phenomena and the course of edema and ischemia.

- Section on Cellular Neuropathology—Henry deF. Webster, M.D.

This section is engaged in immunocytochemical studies on myelin, glial, and viral protein distribution in nervous tissue. This represents a part of broader investigations in this section concerning the pathogenesis of central and peripheral demyelinating diseases of known and unknown cause.

- Section on Functional Neuroanatomy—Thomas S. Reese, M.D.

This section is primarily concerned with studies on synaptic structure and function, redistribution of elements during neuronal activity and secretion, intrinsic membrane proteins and lipids, and neuronal cytoskeleton. Using modern electron optical and low temperature techniques, the structure of neural cells and membranes is investigated in close to molecular level of resolution.

- Section on Neurocytology—Milton W. Brightman, Ph.D.

The section is engaged in studies to delineate the conditions necessary for the placement, survival, regeneration, and function of transplanted neurons—both peripheral and central, to characterize further the tropism between central and peripheral neurons and to analyze the structural changes in muscle and astrocytic cell membranes during degeneration and regeneration.

Laboratory of Neurophysiology—
Jeffery L. Barker, M.D.

All of the laboratory's projects involve multi-disciplinary analysis of the physiological properties of vertebrate central neurons studied *in vitro.* The techniques utilized encompass many of those current in cellular neurobiology, including electrophysiology, immunohistochemistry, electronmicroscopy, biochemistry, and dissociated cell culture. A principle line of investigation is focused on the physiological properties of neurons cultured from different parts of the mammalian CNS, since monolayer cultures allow immediate accessibility to quantitative analysis of neuronal function at the cellular level. Using such a strategy, members of the laboratory are studying which properties are resident in different types of nerve cells, how these properties evolve during embryonic development, and what roles they play in intercellular communication. These studies are thus aimed at providing insight primarily into the question of what types of phenotypic properties are expressed by different CNS cells and secondarily into the related problem of how these properties differentiate the functions of one cell type from another. One long-term goal of the laboratory is a better understanding of the relationship between the activity of ion channels in neuronal membranes and the synthesis and secretion of specific transmitter substances.

Another area of considerable activity in the laboratory involves pharmacological experiments on the cellular mechanisms of actions of clinically important drugs like benzodiazepines, barbituates, and convulsants using electrophysiological recording techniques (voltage-clamp and patch-clamp).

Laboratory of Molecular Biology—
Ernst Freese, Ph.D.

Developmental effects of mutations and drugs are examined. They are correlated to hereditary diseases and teratogenic effects.

- Section on Developmental Biology—Ernst Freese, Ph.D.

The control of cell differentiation is studied in bacteria and yeast using mutations, genetic engineering, and drugs. The developmental effects are examined in terms of metabolism and the control of nucleic acid, enzyme, wall, and membrane synthesis. The molecular changes of nucleic acid, proteins, and membranes are analyzed.

- Section on Molecular Neurobiology—

Studies are designed to further our understanding of the mechanisms by which individual cells respond to external signals. Cell surface receptors for hormones and neurotransmitters, in particular those whose function involve modulation of cAMP levels are investigated using the methods of biochemistry and biology.

Convulsive, Developmental, and Neuromuscular Disorders Program

Epilepsy Branch—

Roger J. Porter, M.D.

This branch develops and coordinates organized and directed research programs on a multi-institutional, geographic, or multidisciplinary basis through its support of five comprehensive programs, each serving a specific geographic area. It develops, conducts, and coordinates collaborative and directed research programs aimed at finding new or improved methods of diagnosis, treatment, and prevention of convulsive disorders. The clinical investigation of new antiepileptic drugs is a major concern. The branch fosters the synthesis, screening, and pharmacologic and metabolic investigation of antiepileptic drugs by collaborative efforts; conducts research on the metabolism of anticonvulsant drugs and the treatment of certain difficult seizure disorders according to rigid protocols within its own facilities; and fosters research in experimental models of epilepsy and improved patient treatment through the use of serum antiepileptic drug determinations.

The Clinical Center

Michael H. Ebert, M.D.
Acting Director

Blood Bank Department—

Paul V. Holland, M.D.

Staff Fellowship

The Blood Bank Department accepts applications for an American Medical Association accredited fellowship program in blood banking and immunohematology. The fellowship assignment can be for 1 or 2 years. Vacancies do not necessarily occur each year. Board certification or eligibility in internal medicine, clinical pathology, or hematology is required.

The program offers training in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. The fellow receives broad experience in all aspects of blood banking, including clinical and laboratory immunohematology, pheresis techniques, donor recruitment, and blood component preparation and therapy. The fellow participates actively in the service and teaching functions of the Blood Bank.

Involvement in a clinical or basic research project is encouraged. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various institutes. Current programs include investigations into the various agents responsible for posttransfusion hepatitis, the effects of biologic incompatibilities on transfusion and transplantation, and immunologic studies of drug-induced hemolytic anemias, and innovative uses of automated pheresis techniques.

Prospective applicants desiring more information should write to Paul V. Holland, M.D., Chief, Blood Bank Department, Building 10A, Room 1E33, National Institutes of Health, Bethesda, Maryland 20205.

Clinical Pathology Department—

Ronald Elin, M.D., Ph.D.

The Clinical Pathology Department offers a broad spectrum of laboratory diagnostic services for intramural patient care for the institutes. The department is organized into three services: clinical chemistry, hematology, and microbiology. In addition, there is a close working relationship with the Information Systems Management Department. The Clinical Chemistry, Hematology, and Microbiology Services and Information Systems Management Department, offer medical staff fellow positions, but not necessarily on a yearly basis.

- Clinical Chemistry—

The Clinical Chemistry Service provides all the chemical diagnostic tests on the patients in the Clinical Center, as well as for outpatient clinics. The senior staff is composed of five individuals with M.D. and/or Ph.D. degrees. Approximately 100,000 tests are performed per month by a technical staff of 42 medical technologists, chemists, technicians, and medical aides. The Clinical Chemistry Service collaborates in clinical research of a chemical nature and conducts extensive research and development in analytic methodology, automation, and computerization. Current interests within the service are the development of radioimmunoassays, adaptation of the calorimeter for laboratory testing, electrophoresis, factors affecting the reference range, instrument evaluation, and automated assay.

A medical staff fellow entering this 2-year program would receive in-depth training in the various aspects of clinical chemistry. The first year of the program would be devoted to a rotation through the clinical chemistry sections—STAT tests, electrophoresis, radioimmunoassay, urinalysis, special chemistry, and SMAC. In addition, emphasis would be placed on the correlation of laboratory data with the status of patients. The fellow would be encouraged to attend working patient rounds and to handle inquiries to the Clinical Chemistry Service from patient-care physicians. Also, during this first year, the fellow would have the opportunity to develop specific interests in investigative studies. During the second year of the program, the fellow would be encouraged to choose a research project for independent investigation under the supervision of a senior staff member or to participate in an ongoing research project.

Any candidate interested in the Medical Staff Fellow Program should write to Ronald J. Elin, M.D., Ph.D., Chief, Chemistry Service, Clinical Pathology Department, Building 10, Room 2C-407, National Institutes of Health, Bethesda, Maryland 20205.

- Hematology

The Hematology Service provides clinical and research experience in hematology. The service is responsible for the operation of the routine clinical hematology, coagulation, and special hematology laboratories. We have an active clinical and consultative service. The Hematology Service also has a research program directed at clinical and basic problems in hematology. Research of particular interest includes coagulation, thrombosis, platelet disorders, advances in morphologic interpretation of bone marrow material, purification and characterization of coagulation proteins, studies on platelet physiology and pathology, and the study of the role of carbohydrates in coagulation and platelet function. Other research endeavors include the use of immunologic and biochemical markers for hematopathologic diagnoses and the development and testing of new procedures of analytic systems in the hematology laboratory.

The Hematology Service recruits medical staff fellows for a minimum of 2 years. Some fellows will spend at least 6 months doing primarily clinical work with patients in the Clinical Center. During this time, the fellow will also have the opportunity to develop a specific interest in investigative studies. Fellows will be encouraged to choose a problem for investigation which can be pursued with the guidance and supervision available in the Hematology Service, a joint project with an established investigator. Medical staff fellows whose primary interest is laboratory research are assigned to highly qualified physicians to provide an opportunity to improve their backgrounds for careers in basic medical research. During their tenure, these fellows will devote most of their time to laboratory research. The candidate who is chosen will be given an opportunity to choose an area of investigation, and a senior staff member will serve as his or her preceptor.

Any candidate interested in either program should write to Harvey R. Gralnick, M.D., Chief, Hematology Service, Clinical Pathology Department, Building 10, Room 2C-390, National Institutes of Health, Bethesda, Maryland 20205.

- Microbiology—

The Microbiology Service provides in-depth training in various aspects of clinical diagnostic microbiology, as well as the opportunity to participate in ongoing developmental research projects. Although the training program is primarily laboratory based, opportunity is considerable for interaction with the Infectious Disease Service and other patient-care physicians. The Microbiology Service is responsible for the isolation and identification of bacterial, mycobacterial, mycologic, and parasitic pathogens in Clinical Center patients. Determinations of antibiotic sensitivity and antibiotic levels are also performed, as well as a variety of clinical serologic procedures. No viral, chlamydial, or rickettsial work is currently performed in our laboratory. Present research activities include the use of computers for the organization and utilization of microbiology laboratory data, the development and assessment of a lysis-filtration and impedance system for blood culturing, and the evaluation of new methodologies for antibiotic sensitivity testing. A variety of clinicopathologic studies is also undertaken or could be initiated under senior staff supervision.

Persons interested in a medical staff fellowship position with the Microbiology Service should contact James D. MacLowry, M.D., Chief, Microbiology Service, Clinical Pathology Department, Building 10, Room 2C-385, National Institutes of Health, Bethesda, Maryland 20205.

- Laboratory Computer—

The Information Systems Management Department provides computer and statistical support for the patient-care and research programs of the Clinical Pathology Department. The service also conducts research on medical laboratory automation, computer-assisted interpretation of clinical laboratory measurements, variation in test results, and methods of quality control. The staff includes pathologists, programmers, and computer operators. In addition to its own minicomputer systems, the service makes extensive use of the NIH IBM 370 and DEC PDP-10 time-sharing computers. Investigators in the service utilize extensive machine-readable files of clinical and laboratory information pertaining to NIH patients.

A medical staff fellow works with the senior staff in applying computer and statistical techniques to problems of laboratory methods. Fellows are encouraged to develop independent or collaborative research projects. In addition, they may participate in teaching conferences of the Clinical Pathology Department.

Interested candidates should write to Thomas L. Lewis, M.D., Associate Director for Information Systems Management, Clinical Center, Building 10, Room 2C-137, National Institutes of Health, Bethesda, Maryland 20205.

Critical Care Medicine Department—

Joseph E. Parrillo, M.D.

The Critical Care Medicine Department is offering 2- to 3-year fellowships in critical care medicine beginning in July 1983. To be eligible, a physician must have completed 3 years of residency in internal medicine, anesthesiology, or general surgery. The fellowship consists of a first year of clinical training in critical care medicine in the intensive care units at the National Institutes of Health and in the medical-surgical intensive care unit at the National Naval Medical Center (Bethesda Naval Hospital). The clinical training provides broad experience in the care of critically ill patients and in a wide variety of procedures necessary to critical care. The second year (and an optional third year for selected fellows) consists of an individually designed program in clinical investigation or basic laboratory research related to critical illnesses. The NIH Fellowship Program is designed to satisfy all the subspecialty Board requirements for critical care medicine. Critical Care Medicine Boards are planned for the first time in 1984.

The fellowship program is designed to provide excellent clinical training in the care of extraordinarily sick patients with multisystem organ dysfunction. Critical care physicians in the NIH ICU have primary responsibility for care of the patient. The critical care physicians work closely with referring physicians and call on multiple consultative services necessary to give full intensive care to these patients. The Critical Care Medicine Department consists of a senior staff that has subspecialty training in cardiology, pulmonary diseases, anesthesiology, infectious diseases, and critical care medicine. The staff performs most of the invasive procedures (Swan Ganz catheterization, cardiac catheterization, bronchoscopy, etc.) themselves in a specially constructed procedure/catheterization laboratory in the ICU. The ICU also has capability for computer processing and analysis, noninvasive (echocardiography, nuclear scanning) cardiac diagnostic studies, and pulmonary function studies.

The fellowship research training is designed to produce independent clinical investigators in the field of critical care medicine. The educational program includes weekly conferences on clinical critical care medicine and seminars regarding ongoing research programs in the department. Each fellow will have a senior staff member guiding the investigations. Ongoing research in the department includes the following: studies of hemodynamics and cardiovascular function in different forms of shock; the immunopathogenesis of septic shock; capillary leak syndromes; pulmonary functional abnormalities in shock lung; studies of immune cellular function in shock lung, asthma, and other forms of severe pulmonary disease; critical care of the immunocompromised host; and studies of immune cellular function and therapy of the acquired immune deficiency syndrome (AIDS).

For further information on the program, please contact Joseph E. Parrillo, M.D., Chief, Critical Care Medicine Department, Building 10, Room 10D48, National Institutes of Health, Bethesda, Maryland 20205.

Diagnostic Radiology Department—

John L. Doppman, M.D.

Staff radiologists are selected each year from among those applicants who have completed their residencies in diagnostic roentgenology. Such appointments are made for a period of 2 years, with opportunity for reappointment.

The department is well equipped to provide the routine and special diagnostic radiographic examinations needed by the 50,000-55,000 patients seen each year. Ultrasound and computed tomography play an increasingly important role in the diagnostic and research activities in the department. The preselection of patients for admission to NIH ensures a challenging and stimulating gamut of diagnostic problems.

Thirteen radiologists comprise the professional staff, and an adequate supporting staff is provided.

Facilities are available for collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

Nuclear Medicine Department—

Steven M. Larson, M.D.

One medical staff fellow is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in nuclear medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved internal medicine, radiology, or clinical pathology is recommended to meet the requirements for certification by the American Board of Nuclear Medicine.

Residency Training

The American Medical Association has approved the department for a 2-year residency training program in nuclear medicine. Qualifications for trainees include at least 2 years of prior training in radiology, pathology, or internal medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital or the Maryland University Hospital.

The department consists of five sections: the Diagnostic Nuclear Medicine Section, the Positron Emission Tomography Section, the Applied Physics Section, the Whole-Body Counter Section, and the Radiopharmacy Section.

The Diagnostic Nuclear Medicine Section provides clinical and investigative service to the physicians of the various institutes working within the Clinical Center. Rectilinear scanners and gamma cameras are the basic imaging devices. Computers for processing nuclear medicine data are located within the section. Computer experts from the Division of Computer Research and Technology (DCRT) provide professional support for the development of computer-assisted nuclear medicine procedures. The Positron Emission Tomography Section provides positron imaging capability for the study of a broad range of conditions. Currently the emphasis has been on brain glucose metabolism in a variety of disease states and in normal conditions. This section is staffed by physicians, radiochemists, and technicians who have the responsibility of cyclotron preparation of positron-emitting radionuclides, radiochemical production of the agents used in the studies, patient and research imaging, and data production and interpretation. The Applied Physics Section and DCRT personnel work cooperatively in the development of new diagnostic techniques. The Whole-Body Counter Section works closely with the Diagnostic Nuclear Medicine Section and the Radiation Safety Branch, Division of Safety, NIH. It operates three whole-body counters and provides a consultation service to all the institutes. It is engaged in basic research on trace quantities of radioactivity, personnel monitoring, and a variety of clinical studies. The staffs of the diagnostic nuclear medicine, positron emission tomography, and whole-body counter sections consist of eight physicians, a radiobiologist, two physicists, two radiochemists, an equipment specialist, eight nuclear medical technicians, four nurses, and three clerks. Departmental professionals are encouraged to interact with members of the various institutes to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases. The Radiopharmacy Section employs four full-time radiopharmacists, a technician, and a clerk to maintain quality control over radiopharmaceuticals used in humans as well as to compound many of the agents used by the Diagnostic Nuclear Medicine Section. This section also provides consultations and support for the use of radionuclides in diagnosis and research.

Division of Computer Research and Technology

Arnold W. Pratt, M.D.,
Director

The Laboratory of Applied Studies, DCRT, offers 2- to 3-year medical staff fellow positions to highly qualified physicians with backgrounds in physical science or engineering (including mathematics through differential equations), 2 years' experience in computer programming, and at least 1 year's clinical experience beyond the M.D. degree.

Laboratory of Applied Studies—
James J. Bailey, M.D.

This laboratory includes mathematicians, physicians, electronics engineers, statisticians, and computer systems analysts engaged in collaborative studies with other biomedical scientists on modeling of physiologic processes, especially transport, reaction-diffusion, and receptor binding kinetics, and with clinicians on applications of image-processing and statistical analysis to the diagnosis of disease and assessment of treatment, particularly in pulmonary and cardiovascular-renal problems.

The division in which this laboratory is located supports the world's most powerful, user-oriented biomedical computing facility. Working on one or more specific projects under the preceptorship of a senior investigator, the medical staff fellow will have ready access to and gain familiarity with advanced interactive display devices, graphics terminals, and programming systems for both clinical and basic research.

Part Four

Academic Programs Available to Medical Staff Fellows

Among the academic programs open to an NIH medical staff fellow are: evening courses provided by the Foundation for Advanced Education in the Sciences, Inc. (FAES); formal seminars under the direction of NIH staff; combined clinical staff conferences; formal lectures; and symposia. The "NIH Calendar of Events" lists 40 to 50 programs each week. Other events of interest are held at universities and institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by the Graduate Program of the FAES, established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science. The foundation is an independent organization whose tuition and fees can be paid by a Federal employer. The FAES also operates the NIH bookstore, which supplies textbooks and other reading material for the convenience of NIH staff.

Courses are offered in two semesters, fall and spring. They are offered at the undergraduate and graduate levels under the programs of several departments of instruction: behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages, and general studies. The FAES and the Clinical Center sponsor board review courses in medicine and pediatrics. Subspecialty courses are offered for board review in endocrinology, hematology, and oncology. Further inquiries regarding the Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education in the Sciences, Inc., National Institutes of Health, Bethesda, Maryland 20205.

Seminars

An NIH program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent investigators and gives them the additional opportunity to master selected topics not adequately covered during college or graduate schooling. These seminars are now administered by the FAES, in conjunction with the evening courses. The program accommodates medical staff fellows involved in clinical or basic research and other properly qualified persons.

A number of tutorial seminars are generally made available each academic year in each of the following categories: biochemistry and genetics, cell biology, immunology, and physiology.

Weekly seminars run from September through January and from February through June. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of an expert in the field. In preparation for these, the medical staff fellow does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate institutes engaged in clinical research, the Clinical Center sponsors at least one monthly combined clinical staff conference for 8 months of the year. Each conference is conducted by one of the institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff and serve to keep individual investigators abreast of current emphasis in all clinical research.

Topics Presented in the 1982-83 Series Were:

December 9, 1982	Samuel Broder, M.D.	Human Retrovirus Associated With T-Cell Leukemia and Lymphoma
January 20, 1983	Michael Kaliner, M.D.	Airway Mucus
January 27, 1983	John I. Gallin, M.D.	Chronic Granulomatous Disease
February 24, 1983	D. Lynn Loriaux, M.D.	LHRH Anologues and Their Use in Clinical Research
March 17, 1983	Alfred D. Steinberg, M.D.	Relevance of Animal Models of Autoimmunity to Human Systemic Erythematosus
April 14, 1983	Harvey R. Gralnick, M.D.	Myelodysplastic Syndrome
May 19, 1983	Bruce J. Baum, D.M.D., Ph.D.	Therapy-Induced Dysfunctions of Salivary Glands
June 2, 1983	N. Raphael Shulman, M.D.	Recent Advances in Platelet Immunology
June 23, 1983	Anthony S. Fauci, M.D.	The Acquired Immunodeficiency Syndrome
July 28, 1983	Ronald G. Crystal, M.D.	Oxidant Injury to the Lungs

Several formal lectures are presented annually. **The National Institutes of Health Lecture Series** was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the scientific directors of the institutes. Dr. Joan A. Steitz of Yale University gave the most recent NIH lecture in November, 1982 on "Autoantibodies as Probes for Small Ribonucleoproteins from Eucaryotes."

The **R. E. Dyer Lectureship** was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942-50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science. Dr. Michael Potter of the National Cancer Institute and Dr. David Davies of the National

Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases presented the 1982 Dyer lecture on "The Three-Dimensional Structure of the Antibody Molecule: Specificity and Diversity." Among other distinguished speakers have been Nobel laureates Dr. Howard M. Temin, who spoke on "The Replication and Possible Origin of RNA Viruses with a DNA Polymerase" and Dr. D. Carleton Gajdusek, who discussed his work on kuru.

The **G. Burroughs Mider Lectureship** was established in 1968 by the scientific directors to honor Dr. Mider for his distinguished service to NIH. On advice of the scientific directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Recent Mider Lectures:

1982	William E. Paul, M.D.	Living with Lymphocytes, or B Lymphocytes and How They Grow
1981	Louis Sokoloff, M.D.	Metabolic Mapping of Local Functional Activity in the Central Nervous System
1980	Thomas Waldmann, M.D.	The Control of the Immune Response Regulatory Cellular Interactions and the Control of Lymphocyte Differentiation
1979	Martha Vaughan, M.D.	Regulation of Cyclic Nucleotide Metabolism
1978	Jesse Roth, M.D.	Receptor Disorders in Man
1977	Philip Leder. M.D.	A Close and Surprising Look at the Mammalian Genome
1977	Maxine F. Singer, Ph.D.	Monkey Business: Sequences in the Monkey Genome and Their Interaction with Simian Virus 40 DNA
1975	Karl A. Piez, Ph.D.	Collagen: Its Chemistry, Structure and Function
1974	Elizabeth F. Neufeld, Ph.D.	Inherited Lysosomal Disorders Studies in Cell Culture

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These, and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Uniformed Services University of the Health Services at the National Naval Medical Center, offer exceptional educational opportunities. Some medical staff fellows augment their experience at NIH with studies at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located on the first floor of the Clinical Center) is an open-stack, self-service library with a collection of some 272,000 volumes of medical and scientific books and journals. Some 2,000 new books and 3,700 journal subscriptions are received annually. An integral part of the research needs of the NIH staff, the NIH library's major subject areas include medicine, health sciences, chemistry, physiology, biology, physics and the peripheral areas of economics, education, legislation, and social sciences. A full range of services is provided NIH employees, including library copy service, manual and on-line bibliographic service, interlibrary loan, advisory consultation for literature needs, and a translating service.

The National Library of Medicine (NLM) is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 3 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service. Access to the library's computerized data base of journal references (MEDLINE) is available both at NLM and at the NIH library.

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☆U.S. GOVERNMENT PRINTING OFFICE:1983-409-8

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NIH Publication No. 83-213
Revised April 1983

20.3015:
85

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DOCUMENTS

Medical Staff Fellowship Program at the National Institutes of Health

1985 Catalog

U.S.
DEPARTMENT
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Public
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of
Health

1984

November 15, 1984	Deadline for receipt of completed NIH Medical Staff Fellow applications
January 7-18, 1985	Interview period
February 6, 1985	Notification to all candidates

Applications may be obtained from:

The NIH Medical Staff Fellowship Program
Building 10, Room 2N220A
National Institutes of Health
Bethesda, MD 20205
Tel: 301-496-2427

The National Institutes of Health does not discriminate in employment on grounds of sex, race, color, age, religion, handicap, or national origin.

Foreword

The National Institutes of Health and the Warren Grant Magnuson Clinical Center, the research hospital for the Institutes, are international centers for biomedical research and clinical investigation. The Clinical Center and the other intramural research facilities in Bethesda have provided research and training opportunities for thousands of foreign scientists and physicians and for an even greater number of research scientists and clinical investigators in this country.

The Clinical Center has 540 beds to which patients are admitted for participation in research protocols. The protocols are directed towards understanding disease as well as towards diagnosis and treatment. The proximity of the wards to the 1,800 research laboratories ensures continuing collaboration between clinical and laboratory scientists. Within this scientific community there are unique opportunities to acquire the skills necessary for biomedical research. This catalog describes the opportunities open to physicians and dentists in the Medical Staff Fellowship Program at the NIH.

John L. Decker, M.D.
Director

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Part One

General Description of Medical Staff Fellowships and Other Opportunities

The Warren Grant Magnuson Clinical Center

John L. Decker, M.D.,
Director

The Warren Grant Magnuson Clinical Center is a modern laboratory hospital facility shared by the 11 Institutes that conduct combined laboratory and clinical study programs. This 540-bed research hospital is located on a 300-acre campus at the National Institutes of Health (NIH) in Bethesda, Maryland.

NIH is the largest biomedical research organization in the world. Approximately 2,600 staff members have doctoral degrees, including almost 1,000 with M.D. degrees, more than 1,500 with Ph.D. degrees, and about 40 with D.D.S. and 50 with D.V.M. degrees. A significant number have more than one doctorate.

Three Nobel laureates work on the campus: Drs. D. Carleton Gajdusek, Julius Axelrod, and Marshall W. Nirenberg. Dr. Gajdusek received the award in 1976 for his work in proving that kuru—a fatal disease affecting the nervous system—is a transmissible slow virus infection.

In 1970, Dr. Axelrod was cited for discoveries concerning transmitter substances in nerve terminals and mechanisms for their storage, release, and deactivation. Dr. Nirenberg was honored in 1968 for his work on the translation of the genetic code and its function in protein synthesis.

Three other scientists received the Nobel prize for work done while at NIH. In 1976, Dr. Baruch Blumberg was honored for his discovery of the "Australia antigen," a marker of hepatitis B. The prize was given to Dr. Christian Anfinsen in 1972 for his studies of ribonuclease, particularly the relationship between amino acid sequences and the conformation of enzyme molecules. Dr. Arthur Kornberg received the award in 1959 for his research on the mechanisms in the biological synthesis of DNA and RNA.

With the help of a staff of almost 3,000 technical personnel, NIH scientists are involved in some 2,500 research projects which result in more than 5,000 published scientific articles each year. The budget for this intramural research effort is approximately $486 million.

The 14-story Clinical Center represents an important resource for training in medical research. The hospital provides a setting in which a young physician can participate in medical care, acquire new clinical skills, and carry out research in a laboratory conveniently located a few steps from the patient's room. The center is designed to bring scientists working in laboratories into close proximity with clinicians caring for patients so that bench investigators and physi-

cians may collaborate on problem diseases.

The primary mission of the Clinical Center is to provide a specialized form of hospital care necessary for Institute studies. To accomplish this goal, the Clinical Center has developed patient care programs and related technical support systems which stand at the fore of modern health care.

The Nuclear Medicine Department provides whole-body scanning and diagnostic imaging through the use of radioactive pharmaceuticals. Positron emission tomography and radionuclide cineangiography are among the imaging techniques under study. The Diagnostic Radiology Department has a full complement of radiological equipment, including CAT scanners and ultrasonic scanners. Nuclear magnetic resonance and digital fluorographic devices are among those the department plans to acquire and evaluate. The superbly equipped clinical pathology laboratories provide optimum support to physicians and their patients. The Blood Bank provides blood products for the patients, teaches blood banking and immunohematology, and conducts research.

Numerous opportunities are available for medical staff fellows to participate in the use and development of modern medical computer systems, medical instrumentation and electronics. These systems are used for patient care, for clinical and basic research, and for the education of staff fellows in the use of computers in medicine.

A large, computer-based Medical Information and Communication System is used in support of patient care in the Clinical Center and the adjoining Ambulatory Care Research Facility. Two hundred display terminals and 85 printers are located on the Clinical Center nursing units and in-service department areas to permit rapid retrieval of patient information and processing of medical orders. This system is used by physicians, nurses, and other medical professionals as part of their daily patient care activities. In addition, information obtained during the patient care process is available through the central NIH computer facility for retrieval and research analysis.

The Clinical Center admits approximately 8,000 patients yearly. In addition, the outpatient clinics service over 127,000 patient visits annually.

A newly completed 13-story Ambulatory Care Research Facility (ACRF), adjacent to the original Clinical Center structure, is designed to expand and strengthen the combined laboratory and patient care programs of the Clinical Center. It is estimated that the new wing will double the Clinical Center's outpatient capacity. The facility will provide an optimum environment to care for and study outpatients, yet it will retain the same proximity between clinical and laboratory scientists that has successfully promoted medical inquiry in the existing Clinical Center.

The Clinical Center appoints medical staff fellows for the Departments of Clinical Pathology, Critical Care Medicine, Nuclear Medicine, Diagnostic Radiology, and the Blood Bank. These programs are described in part three.

The Medical Staff Fellowship Program

Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists through appointments as medical staff fellows at the National Institutes of Health. These positions encompass most medical specialties and basic science disciplines.

Appointments to the Medical Staff Fellowship Program (formerly the Associate Training Program and encompassing what used to be designated clinical, research, and staff associate positions) are based on professional attainment, research interest, and ability. The NIH seeks outstanding candidates and selection is made without regard to race, sex, geographical location, or university affiliation. Candidates may be selected because of demonstrated excellence in research or in a clinical discipline. Selections are made through a matching process explained in part two.

Each medical staff fellow participates in a research program under the direction of a preceptor. Preceptors, drawn from a large number of skilled investigators, serve to enrich each staff fellow's experience. Because of the unique blending of clinical and nonclinical scientists, the staff fellow is in daily contact with scholars representing a variety of research interests.

The NIH offers many educational opportunities ranging from tutorials to sponsored lectureships. Postgraduate instruction, sponsored by the Clinical Center or the graduate program of the Foundation for Advanced Education in the Sciences, Inc., is available on a broad range of topics, including mathematics, languages, laboratory skills, and clinical reviews (see part four).

The NIH affords the medical staff fellow the opportunity to participate in clinical and laboratory research. Clinical activities are carried out near laboratory facilities and are under the immediate supervision of senior investigators. This proximity to patients and to collaborating scientists from many biological disciplines has created a superb environment for learning and performance of clinical research.

Some fellows devote most of their time to laboratory research in a biomedical science. The preceptor is responsible for training in research methods and design, and for guidance in the conduct of specific research undertakings and in the interpretation of results. One of the goals of the program is to select research problems which will enable the staff fellow to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The medical staff fellow position also provides opportunities for those highly qualified candidates who could contribute significantly to research areas not specifically designated in the research or clinical categories. In these cases, the staff fellow may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom he or she works. Research experience may be supplemented by attending formal evening study courses, lectures by guest speakers and a variety of medical seminars.

The Dental Staff Fellow

Like medical staff fellows, the dental staff fellow may participate in laboratory and clinical research, and enhance professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the fellowship, there is full opportunity for a fellow to become familiar with all ongoing research programs relevant to dentistry; affiliate with one or more preceptors to participate in a mutually acceptable area of investigation; and extend scientific background through rounds, conferences, seminars, and formalized course work.

The Medical Staff Fellow in Pharmacology (Pharmacology Research Associate Program)

Staff fellows in this program, sponsored by the National Institute of General Medical Sciences, spend most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those committed to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

Staff Physicians

Some physicians, already qualified in a specialty, are not appointed as medical staff fellows but as staff physicians. Initial appointments are temporary and usually for 2 years, but some staff physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part-time in research.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to medical students. For 1984-85, the staffs of several Institutes are collaborating to supply an in-depth exposure to 15 clinical subspecialties: anesthesiology, clinical dental care, critical care medicine, computers in clinical medicine, endocrinology and metabolism, genetics, geriatrics, immunology, medical-surgical neurology, neurobiology, nuclear medicine, oncology-hematology, psychopharmacology, pediatric psychopharmacology, and surgical oncology.

The essence of this educational experience is close association between the student, staff fellows, and physician-scientists in several of the Institutes.

Students are assigned patients for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with interests in fields other than those listed above are sometimes arranged through communication between an NIH staff member and a faculty sponsor of the students.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Clinical Electives Program Office
Building 10, Room 2N220A
National Institutes of Health
Bethesda, MD 20205

Approved Training Programs

Residency training programs approved by the Accrediting Council on Graduate Medical Education are offered in anatomical pathology and nuclear medicine as are fellowships for advanced subspecialty training in blood banking, and clinical pathology, including clinical chemistry, hematology, and microbiology, and the laboratory computer service.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Lance A. Liotta, M.D., Ph.D.
Chief, Laboratory of Pathology
Building 10, Room 2A33
National Institutes of Health
Bethesda, MD 20205

Steven M. Larson, M.D.
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National Institutes of Health
Bethesda, MD 20205

Board Certification: The first year of the clinical fellowship in the National Heart, Lung, and Blood Institute is accredited as a third year of training in internal medicine by the American Board of Internal Medicine. The 3-year medical staff fellowship has been accepted for training by the subspecialty board in Infectious Diseases and the conjoint Board of Allergy and Immunology.

Credit towards board certification is offered in the following specialties and subspecialties:

Allergy
Blood banking
Clinical chemistry
Critical care medicine
Dermatology
Endocrinology
Hematology
Gastroenterology
Genetics
Infectious diseases
Internal medicine (NHLBI only)
Medical oncology
Microbiology
Neurology
Pediatric endocrinology
Pediatric genetics
Pediatric hematology/oncology
Pediatrics
Psychiatry
Reproductive endocrinology
  (obstetrics and gynecology)
Rheumatology

The amount of credit earned depends on the training completed and the acceptability of such to the individual board. Candidates are advised to consult the appropriate Institute and specific subspecialty board for additional information.

Endocrinology Fellowship Program

The NIH Endocrinology Fellowship Program is an interinstitute program which involves most of the clinical branches working in this field on the campus at Bethesda. It is devised for physicians who seek a broad experience in both fundamental research and clinical experience in endocrinology. Fellows are selected for a period of 2 or 3 years which includes approximately 1 year of clinical activity among several endocrinology branches of the NIH. During this clinical period, fellows function as primary care physicians for the 70-bed endocrinology inpatient services, serve as consultants for other services of the 540-bed Clinical Center as well as for other local hospitals, and participate in outpatient work, rounds, and seminars. The remainder of the time is spent primarily in laboratory investigation under the direction of a senior investigator in one of the endocrinology branches. During this research period opportunity exists for continuing outpatient work and participation in clinical conferences. No position will be offered for a single year.

Medical staff fellows selected by any of the three endocrinology branches of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (Clinical Endocrinology, Diabetes, or Metabolic Diseases) as well as the Developmental Endocrinology Branch of the National Institute of Child Health and Human Development automatically participate in the interinstitute program. Medical staff fellows from other branches may participate only under special circumstances. The National Heart, Lung, and Blood Institute also participates in the interinstitute program.

Lectures and Courses

The NIH campus provides a stimulating intellectual environment for continuing education, including multiple clinical and basic science conferences and journal clubs, as well as tutorial seminars and courses spanning many disciplines. The endocrinology fellowship program sponsors formal endocrinology seminars and lecture series covering the field broadly and in detail. The Computer Science Division and Radiation Safety Branch provide detailed practical work and study in these fields. The latter branch gives an intensive course in the use of radionuclides, enabling graduates to apply for their own radioisotope license after completion of the fellowship.

Medical Student Program
Students selected from various medical schools throughout the country participate in endocrinology courses offered three times yearly. Fellows work in close association with the students and supervise their patient care activities. These and other teaching functions help develop the fellows' skills as educators in preparation for later academic careers.

Internal Medicine and Endocrinology Board Examinations
Studies in the Clinical Center relate to all areas of internal medicine, and fellows are encouraged to develop their general clinical skills. Completion of the fellowship program satisfies requirements for the Endocrinology Subspecialty Board Examination. Because of recent changes in the requirements for the Certifying Examination of Internal Medicine, applicants are encouraged to review their residency training plans directly with the Board.

Prospective applicants who would like further information on the program should write Bruce D. Weintraub, M.D., Building 10, Room 8N315, National Institutes of Health, Bethesda, MD 20205.

Medical Genetics Program

The NIH Interinstitute Medical Genetics Program is a cooperative undertaking involving several clinical branches and research laboratories in various Institutes located on the Bethesda campus. It is a program of 2-, or in some cases, 3-years' duration for physicians seeking broad exposure to both research and clinical experience in human genetics. The training is designed to fulfill all requirements of the American Board of Medical Genetics for fellowships leading to eligibility for Board certification.

The fellowship includes clinical activities and laboratory or clinical investigations under the direction of a senior scientist. Fellows are responsible for outpatients seen at the weekly NIH Genetics Clinic. They also serve as genetics consultants in the 540-bed Clinical Center and participate in weekly patient conferences and ward rounds. Further opportunities to become familiar with the spectrum of patients with genetic disease are provided by optional attendance at genetics clinics at collaborating institutions including the Johns Hopkins Hospital, George Washington University Pediatric Genetics Clinic, and Wilson Unit (Prenatal Diagnosis).

Entrance into the Medical Genetics Program is through either of two routes: fellows may be accepted directly into it, and then later choose a laboratory in which to do research; or, alternatively, fellows may be selected by a research branch or laboratory in one of the participating institutes and then apply for acceptance into the Medical Genetics Program. Candidates choosing the second route must indicate their interest in the Medical Genetics Program on the medical staff fellowship application form; they will then be interviewed by the program's steering committee as well as by scientists from the research branches to which they have applied.

Fellows in the Medical Genetics Program pursue research chosen from many types of investigations related to genetic diseases; descriptions of the diverse interests of participating scientists are provided in a brochure which will be supplied to fellowship applicants. The aim of this program is to provide fellows with research experiences of the highest caliber and to prepare them for careers as independent investigators in medical genetics.

The fellowship program includes a seminar series in medical genetics in which invited speakers discuss research and clinical topics of current interest, and a journal club. Other opportunities for continuing education (clinical and basic science conferences, tutorial seminars and postgraduate courses) are plentiful on the NIH campus. The fellowship program also sponsors a yearly 8-week elective in medical genetics for senior students from medical schools around the country; fellows assist in didactic lecture-demonstrations on the approach to patients with genetic diseases and in supervision of students in patient-related activities. These and other teaching opportunities develop the fellows' skills as educators in preparation for academic careers.

Applications for the program should be directed to the Medical Staff Fellowship Office (see p. 9). Further information may be obtained by telephone from Drs. John J. Mulvihill, or Dilys M. Parry at (301) 496-4947.

Part Two

Applying for a Medical Staff Fellowship

About 125 medical staff fellows are appointed annually to positions emphasizing clinical or basic research. Fellows are employed through the Public Health Service (PHS) in special civil service appointments, but not in the Commissioned Corps of the PHS.

Minimum eligibility requirements for most medical staff fellowships is completion of 2 years of graduate medical training before entrance on duty. Application should be made between 1 and 2 years before desired date of appointment.

To be considered for a medical staff fellowship, completed application forms must be received in the NIH Medical Staff Fellowship Office, Building 10, Room 2N220A, National Institutes of Health, Bethesda, MD 20205, by November 15, 1984.

Participants in the National Health Service Corps Scholarship Program are not eligible for consideration until after they have served obligated pay-back years in NHSC-designated areas of medical need.

To be eligible for a PHS appointment as a medical staff fellow (not in the Commissioned Corps), a candidate must meet the following requirements:

- Be a United States citizen or a permanent U.S. resident.
- Meet the medical fitness standards.
- Be a graduate of an accredited medical, osteopathic, or dental school.
- Satisfactorily complete an internship (PG1) approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)
- Foreign medical graduates—foreign nationals or American citizens who have received their medical degree from a medical school outside the United States, Puerto Rico, and Canada and that is listed in the World Health Organization's *World Directory of Medical Schools*—must be certified by the Educational Commission for Foreign Medical Graduates (ECFMG). ECFMG certification may presently be obtained by passing the ECFMG examination, the Visa Qualifying Examination (VQE) or the Federal Licensing Examination (FLEX). A new two-day Foreign Medical Graduate Examination in the Medical Sciences (FMGEMS) will be administered for the first time in July 1984. FMGEMS will replace the present ECFMG and VQE examinations.

Employment Benefits for Medical Staff Fellows

Medical staff fellows are entitled to the following benefits which are comparable to those offered to Civil Service employees: partial subsidy for health insurance and group life insurance, retirement benefits, occupational medical emergency service at NIH, compensation for injury, 13 working days of annual leave per year and the same amount of sick leave, and training at Government expense. Medical staff fellows will be paid for entry-on-duty travel to NIH and shipment of household goods. Return travel and shipping will also be paid to fellows who leave after completion of their initial assignment.

Method of Selection—
Matching Program

Selections for medical staff fellow appointments are made through a matching process in which the candidate's preferences are matched with the Institute's preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Checklist." After reading part three of this catalog, the candidate should check off on these sheets the areas in which he or she is interested. There is no limit to the number of interest areas which may be checked. The application will be sent to all laboratories and branches which the candidate has checked.

After thorough review by the Institutes of all applications, a limited number of candidates will be selected for personal interviews after which the candidate submits his or her confidential preference list. *Applicants should only list programs in which they have an interest and would accept if chosen. In a highly competitive selection system, failure to accept a position after the "match" compromises another candidate's opportunities.*

The NIH Medical Staff Fellowship Office will set up the interview and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

Part Three

Program Areas for Which Candidates May Apply

Each of the major NIH components has prepared a description of its program areas for which medical staff fellows may seek appointment. These descriptions are meant to anticipate many of the questions applicants may have in selecting program areas for which they wish to be considered. *It should be noted that a candidate is not limited as to the number of kinds of positions for which he or she may apply.*

National Cancer Institute

Vincent T. DeVita, Jr., M.D.,
Director and Clinical Director

Division of Cancer Biology and Diagnosis

—Alan S. Rabson, M.D., Director

The Division of Cancer Biology and Diagnosis is broadly concerned with biochemical, genetic, physiologic, immunologic, and metabolic derangements that predispose organisms to neoplasia and that result from neoplasia. Within this area, a wide variety of research interests are pursued which involve basic questions of immunology, virology, molecular biology, and biochemistry of normal and pathologic states.

The Division is composed of several branches and laboratories, each under the direction of a branch or laboratory chief. Medical staff fellow positions are available in many of these areas and fellows work exclusively with the branch or laboratory in which they are accepted. All fellows have a unique opportunity to become experienced scientists in their fields of interest and thereby initiate a career in academic medicine and research.

Appointments in Clinical Research

Clinical positions are available for medical staff fellows in the Metabolism Branch, Immunology Branch, Dermatology Branch, and the Laboratory of Pathology. Fellows participate in patient care directly related to the research interests of the branch and engage in general research under the direction of individual scientists. The scope and orientation of each of these positions depends, of course, on that of the particular branch or laboratory.

Appointments in Laboratory Research

Nonclinical positions are available in the following laboratories: Biochemistry, Pathophysiology, Molecular Biology, Immunobiology, Cell Biology, Genetics, Mathematical Biology, Tumor Immunology and Biology, and Cellular Oncology.

In general, fellows are engaged in original research under guidance of individual investigators who act as preceptors for the fellows.

Clinical Research Branches

Dermatology Branch—
Stephen I. Katz, M.D., Ph.D.

The Dermatology Branch studies the growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic, neoplastic, and inflammatory states; protein synthesis by epithelium, especially of tonofilaments, keratohyalin, and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; physiology of lymphoreticular cells and lymphokine formation; and the biological activity of oncogenic viruses.

Also studied are experimental allergic contact dermatitis; scanning and transmission microscopy of normal and diseased skin and other tissues; scanning microscopy of the cell-surface structure in relation to the mitotic cycle and motility; genodermatoses; biochemical and ultrastructural aspects of melanogenesis in normal and melanoma tissue; biochemistry and keratinization; xeroderma pigmentosum, an inherited disease of sun sensitivity, and multiple cutaneous cancer with abnormal DNA repair; clinical, chemical, and ultrastructural effects of vitamin A on skin; the oncogenic potential of tumor viruses; the development of therapy of epithelial cancers, skin lymphomas, and keratinizing diseases of the skin.

Immunology Branch—
David H. Sachs, M.D.
Senior Investigators

- Howard B. Dickler, M.D.
  Ronald E. Gress, M.D.
  Maryanna P. Henkart, Ph.D.
  Pierre A. Henkart, Ph.D.
  David M. Segal, Ph.D.
  J. Stephen Shaw, M.D.
  Gene M. Shearer, Ph.D.
  Alfred Singer, M.D.
  Dinah S. Singer, Ph.D.
  John R. Wunderlich, M.D.
- Immunotherapy Section—
  Richard J. Hodes, M.D.
- Transplantation Biology Section—
  David H. Sachs, M.D.
  Jeffrey A. Bluestone, Ph.D.

The Immunology Branch is concerned with the chemistry, genetics, biology, and clinical significance of immunity. Cellular immunity, transplantation immunity, and the nature of mammalian cell surfaces are the fundamental areas developed within the branch. Information derived from each of these areas is applied to studies of the relationship between the immune system and neoplastic cells in experimental animals and man.

Biochemical, biophysical, genetic, biological, and clinical investigative techniques are utilized in these studies.

Cellular Immunity—The cell-mediated immune responses of laboratory animals and human beings are being investigated. The responses studied *in vitro* include cellular proliferation, cell-mediated cytotoxicity, and antibody production. Immune mechanisms which could be relevant for autologous neoplastic cell rejection are investigated. Immunity to chemically modified autologous cell-surface antigens, to autologous cells infected with influenza virus, immunity of F_1 hybrid cells to parental antigens, and cellular immune responses to cultured/ syngeneic tumor cell lines represent the models under study. The role played by the major histocompatibility complex (MHC) both with respect to the MHC-product-associated immunogenic complexes found and to

MHC as well as non-MHC immune response genes controlling reactivity to these immunogenic complexes is under investigation.

The immunosuppressive events associated with and leading to the newly discovered acquired immune deficiency syndrome (AIDS) are being investigated by studying the *in vivo* immune potential of human peripheral blood leukocytes, and by using *in vitro* and *in vivo* murine immune models. Particular emphasis is being placed on the possible synergistic effects of virus, exposure of the lymphoid system to sperm, and the suppressive and stimulatory signals associated with *in vivo* allogeneic lymphocyte reactions.

The nature of regulatory influences on the cell-mediated immune response to transplantation antigens is being investigated. Both synergizing and suppressive lymphoid subpopulations have been characterized in *in vitro* systems. Further work is being directed at the mechanisms of such regulatory influences, the role and expression of products of the *I* region of the MHC in these events, and the potential relevance to *in vivo* phenomena including transplantation and tumor immunity.

The mechanisms by which cytotoxic T lymphocytes and NK cells kill specific target cells are also under investigation. Cytoplasmic granules purified from these killer lymphocytes have been shown to be highly cytolytic. The role of these granules in cytotoxic lymphocyte mechanisms is being probed by molecular characterization of the granule components. The ability of the granule to form pores in membranes is being studied using liposomes and by electron microscopy.

The receptors for immune complexes (Fc receptors) on different immunocompetent cell populations are being characterized by a variety of methods. The interactions of these receptors to antigens determined by the immune response gene region of the MHC (Ia antigens), surface IgM and IgD, as well as to other cell-surface molecules are being investigated. The role of this receptor and these interactions in the immune response and the regulatory role of antibody are currently being studied.

Humoral Immunity—A number of *in vitro* assays have been developed and characterized in the mouse including: primary and secondary antibody plaque-forming cell assays, T-cell proliferation assays, and antibody-secretion-enzyme linked immunoassay for use with a variety of antigens, including those under genetic control; and T-lymphocyte and accessory cell independent B-cell responses to antibodies specific for antigen receptors plus T-cell replacing factor(s). These assays are being used to evaluate the cellular level of expression of immune response genes and the mode of action of such genes; to evaluate the role of cell-surface antigens determined by the *I* region of the H-2 complex and the role of subpopulations of cells bearing these antigens; to characterize the nature and mechanism of action of antigen-specific helper and suppressor factors; to evaluate the immunologic role of idiotype-bearing molecules of both T- and B-lymphocyte origin; and to use purified factors and monoclonal antibodies to characterize the cell-surface molecules responsible for triggering and/or regulation of responses. Antibodies to idiotypic specificities of antibodies, the levels of which are regulated by immune-response genes, have been shown to activate directly both helper T-lymphocytes and B-lymphocytes.

Transplantation Immunity—Antibodies against histocompatibility antigens and tumor antigens are used as reagents for determining the nature of these antigens and manipulating the immune response against them. Studies utilize inbred rats and mice and congenic mice. Strains of miniature swine have been developed to provide large quantities of materials for chemical characterization of surface antigens and as a model for organ transplantation studies.

Antibodies with specificities directed against transplantation antigens are being examined for chemical and immunologic individuality. Mouse lymphocyte alloantigens determined by genes in the *Ir* region (Ia antigens) are being studied serologically and functionally. Hybridomas producing monoclonal anti-H-2 and anti-Ia antibodies are being produced and characterized. Receptors of these antibodies are being examined for unique and for shared idiotypes.

Cytotoxic T lymphocyte clones are being generated and characterized. These clones are being used to study T cell receptors for MHC alloantigens.

Anti-idiotypic antibodies against mAbs and T cells are being used to modify immune responses to transplantation antigens.

Human allogeneic T-cell responses are being used as a probe to define new antigens in the HLA regions, and to begin to define minor histocompatibility antigens. Cloning of such T cells and their analysis with HLA-mutant cell lines allows precise genetic analysis. New gene products already defined by this approach are being studied for their relevance in regulating human immune responses and for association with human diseases.

New approaches to bone marrow transplantation are being explored. These include the use of monoclonal antibodies to eliminate GVH-producing donor cells. Such approaches are being evaluated in animal models and at the clinical level.

Immunochemistry—The structural and biological consequences of antigen-antibody interactions are being examined by using affinity cross-linked oligomers of IgG antibodies as models for naturally occurring immune complexes. The oligomers are being used to characterize immunoglobulin receptors on various cell types, to assess the effects of antibody polyvalency on cell binding, and to study the physiological consequences of the interactions of cross-linked immunoglobulins with cells. Affinity cross-linked oligomers are also being used to study the interaction of complement with IgG antibodies.

Tumor Immunology—Cellular immune mechanisms of tumor-bearing animals and patients with a variety of malignancies are studied, and attempts are made to modify reactions so as to improve tumor cell kill. Specific assays are established to determine the presence of humoral and cell-mediated responses of hosts to tumors.

Alternative assays are being tested for use in detecting early events in the recognition of malignant cells by host immune lymphoid cells. By means of such assays, attempts will be made to define at a structural level the characteristics of tumor cell-surface antigens which render these cells either susceptible or resistant to immune destruction in the tumor-bearing hosts.

Immunotherapy of tumors is approached both in animal models and patients using nonspecific and specific stimulation of the immune system. A clinical study is in progress to evaluate the effectiveness of adjuvant therapy in preventing recurrence of malignant melanoma in patients who have been rendered clinically free of disease but who have poor prognosis in the absence of therapy. Comparison is being made between adjuvant chemotherapy with methyl-CCNU and immunotherapy with either BCG alone or BCG plus a vaccine of neuraminidase-treated allogeneic melanoma cells.

Molecular Immunology

The molecular mechanisms that regulate the generation of polymorphism and expression of histocompatibility genes are currently being investigated. Using recombinant DNA technology, individual members of the MHC multigene family have been isolated. Analysis of their primary DNA sequences is in progress in order to investigate mechanisms generating diversity. Introduction of isolated MHC genes into cells results in the expression of the heterologous MHC antigen on the host cell surface, providing a system in which to study the regulation of expression of these MHC genes. We have already demonstrated that the transfected MHC gene is subject to regulatory constraints indistinguishable from those of endogenous MHC genes. For example, interferon treatment of the transformed cells resulted in enhanced transcription of both heterologous and endogenous MHC genes. Current efforts are directed toward identifying cellular and extracellular factors which affect MHC gene expression and their cognate DNA sequences. Such studies should shed light on the effect of modulation of MHC antigen expression on immune mechanisms during disease processes.

Metabolism Branch—
Thomas A. Waldmann, M.D.
- Cellular Immunology Section—
  R. Michael Blaese, M.D.
- Endocrine Section—
  James M. Phang, M.D.

The Metabolism Branch is broadly concerned with clinical and laboratory studies that focus on the immunologic, endocrinologic, and metabolic bases of disease occurring in patients with neoplasia.

Immunologic interests encompass a broad area of immunological investigations. These studies are directed toward defining the factors involved in the control of the human immune response.

Major efforts in this area are directed toward: studies of the arrangement of immunoglobulin genes and the gene rearrangements and deletions that are involved in the control of immunoglobulin synthesis; the genetic control of the immune response especially as related to immune response genes including the relationship between HLA antigens and disease and genetic factors controlling the response to complex chemically defined proteins; identification of unique cell surface determinants, especially receptors for growth factors on subpopulations of lymphoid cells with different functional capabilities using antibodies developed with hybridoma technology; characterization of the function and structure of the receptor for T cell growth factor and cloning of the gene for this inducible cell surface receptor; analysis of action of immunoregulatory cells including helper T cells, suppressor T cells and macrophages that regulate antibody responses and on studies of disorders of these immunoregulatory cell interactions in patients with immune dysfunction; studies of the immune response including the generation of specific antibodies and cytotoxic cells to viruses; the isolation and characterization of biological modifiers that suppress the human immune response that are produced *in vivo* or by T cell lines and T-T cell hybridomas; and studies of immune regulation, including factors controlling helper and suppressor T-cell function immunodeficiency states (hypogammaglobulinemia, IgA deficiency, Wiskott-Aldrich syndrome, and ataxia telangiectasia), in leukemias of T-cells, as well as in animal models of disordered immunity.

Endocrine interests include biochemical studies of amino acid metabolism related to collagen synthesis and gluconeogenesis (studies of regulation of enzymes in the collagen synthetic pathway and the proline degradative pathway). These are related to studies of patients with disorders of metabolic bone disease, diabetes mellitus, and amino-acidopathies. Studies of growth hormone, somatomedin, and other growth peptides and their cellular receptors are related to studies of patients with growth disorders.

Basic Research Laboratories

Laboratory of Biochemistry—
Maxine Singer, Ph.D.

The emphasis of the work in the laboratory is on the relation between structure and function in biological systems and on the regulation of cellular processes. The research involves prokaryotes and a range of eukaryote systems selected because of their potential for yielding important information on cellular structure, function, regulation, development, and differentiation. The study of regulation encompasses regulation of gene expression, regulation by interaction of macromolecules, and regulation of cells by hormones and ions.

Work is carried out on both the molecular and cellular level. Techniques include those of biochemistry, physical chemistry, cell biology, and molecular genetics.

- Biosynthesis Section—
  Edward L. Kuff, M.D., Ph.D.

Studies on the evolution and functional significance of endogenous retroviral genetic elements, the enzymatic mechanism of DNA synthesis, and the regulation of collagen biosynthesis and secretion in normal and transformed cells are the concern of this section. Technical approaches include analysis of nucleic acid sequence relationships and genomic organization, isolation of subcellular and viral components, purification of DNA polymerases and their use in constructing *in vitro* synthetic systems, and the characterization of enzymes and cofactors involved in sequential processing of newly formed collagen.

- Cellular Regulation Section—
  O. Wesley McBride, M.D.

Regulation and control of gene expression in eukaryotes is studied using bovine papilloma virus and simian virus 40 as vectors for animal cells and yeast plasmids. Expression vectors are constructed using recombinant DNA techniques, and control of gene expression is evaluated at the levels of both transcription and translation. In other studies, chromosome- and DNA-mediated gene transfer into heterologous mammalian cells is used to map human genes and to isolate restricted regions of the human genome. Somatic cell hybrids are employed to map various human genes, including immunoglobulin genes, to specific chromosome segments.

- Developmental Biochemistry Section—
  Maxine Singer, Ph.D., Acting

Studies on the biochemical processes in development and differentiation are investigated with particular emphasis on regulatory phenomena. The structure of selected components of the genome of several animal species is studied, as well as gene expression during the development of germ cells and embryos. Currently under study are the functional significance of the organization of chromatin in *Drosophila* and genes encoding muscle-specific proteins in chickens.

- Macromolecular Interactions—
  Claude B. Klee, M.D.

Studies are directed toward the understanding of the mechanism of coupled regulation of cellular processes by Ca^{2+}, calmodulin, and cyclic nucleotides. Enzymes regulated by calmodulin are characterized, and then interaction with calmodulin and other regulatory ligands are studied at the molecular level as well as in eukaryotic cells in tissue culture.

- Nucleic Acid Enzymology Section—
  Maxine Singer, Ph.D.

Studies pertain to a variety of nucleic acid structural and functional relationships in eukaryotic cells and viruses. Of particular interest is the organization of repetitive sequences in primate DNA, and the relation between the genomes of simian virus 40 and its permissive host.

- Protein Chemistry Section—
  Elbert A. Peterson, Ph.D.

Studies are in progress on the biochemical changes accompanying differentiation and maturation of leukocytes and the nature of factors controlling these processes; the interactions between cells involved in the immune response and the identification and isolation of participating cell types; and the development of new physical and immunological methods for the purification of cell populations, subcellular organelles, and proteins.

- Office of the Chief—

The laboratory conducts investigations to identify and characterize, and further to isolate and purify, tumor specific antigens using model systems in experimental animals. These studies require the use of immunologic, biochemical, somatic cell hybridization, gene cloning and monoclonal antibody production techniques. Studies include immunologic responses to tumor specific antigens both solubilized and soluble, obtained from spontaneous, chemically and virally induced neoplasms. Studies also involve identification of the genetic elements involved in tumorigenesis and in the induction of tumor specific antigens and the relationship between tumor induction and tumor antigens, using transfection techniques.

- Chemistry Section—
  Ettore Appella, M.D.

This section focuses on different aspects of chemical immunology. One aim is to define the molecular nature of the unique transplantation antigens found among different tumors. This study involves the biochemical purification of such antigens, their chemical structure and gene cloning, and their role in tumor rejection. A second aspect is an investigation of the role played by the Class I and Class II histocompatibility antigens, both in the recognition of different antigens and the control of malignancy. This is being approached by site-directed chemical mutagenesis of cloned histocompatibility genes and expression of the mutant gene in L-cells. A third investigation is a basic approach to the problem of growth control by different transforming proteins using chemical synthesis.

Laboratory of Immunobiology—
Tibor Borsos, Sc.D.

- Section on Cellular Immunity—
  Berton Zbar, M.D.

Cell-mediated immunologic reactions are studied for their capacity to inhibit the growth and spread of experimental cancers. Mycobacterial adjuvants and murine retroviruses are used to augment host response to tumor cells. A variety of animal and *in vitro* models are being used in attempts to delineate the mechanisms of these reactions.

- Section on Humoral Immunity—
  Tibor Borsos, Sc.D.

Antibody- and complement-mediated cytotoxic reactions are studied for the mechanism of action. The primary goal is to understand the molecular basis of complement action and the molecular basis of cell defense mechanism against complement attack. Purification of antibodies, complement components, cell membrane receptors, and studies of synthetic pathways that control cell membrane integrity are also part of the study.

- Section on Immunopathology—
  Edward J. Leonard, M.D.

Alterations in cellular immune function in pathological conditions are studied. Projects include mechanisms of macrophage activation, serum factors that alter macrophage function, the nature of depressed mononuclear phagocyte chemotaxis in patients and animals with neoplasms, the mechanisms of basophil accumulation in delayed hypersensitivity reactions, and the production and chemical nature of lymphotoxin.

Laboratory of Molecular Biology—
Ira Pastan, M.D.

- Molecular Biology Section—
  Ira Pastan, M.D.

This section studies how hormones, viruses, and toxins enter cells and how intracellular sorting and processing of these molecules occurs. This information is currently being applied to new methods of cancer treatment using monoclonal antibodies and immunotoxins. Studies are also carried out on how drugs used in cancer treatment enter cells and on the molecular and biochemical basis of drug resistance in human cancer. Using molecular cloning techniques, the structure and function of genes encoding receptors for hormones and growth factors is being studied. Biochemical experiments are carried out on how transforming proteins such as the transforming protein of Rous sarcoma virus, $p60^{src}$, control cell behavior, cell growth, and gene expression.

- Biochemical Genetics Section—
  Max Gottesman, M.D.

This section studies the regulation of gene expression in *E. coli* and the bacteriophage lambda, including analyses of the control of transcription initiation, transcription termination, and the stability of proteins in bacteria; DNA recombination in prokaryotes with emphasis on site-specific recombination by the bacteriophage lambda and on transposon excision stimulated by phage P; and the construction of new cloning vectors based on the above studies.

- Gene Regulation Section—
  Benoit de Crombrugghe, M.D.

This section studies the developmental control of eukaryotic genes including the identification of their regulatory signals, the genetic and biochemical characterizations of their control mechanisms and the effects of transforming proteins on their expression. Particular emphasis is placed on the collagen genes, a family of developmentally regulated genes. Methods include DNA cloning, gene transfer and selection of mutants.

- Cell Organization Section—
  Seymour Wollman, Ph.D.

Studies are carried out on cellular ultrastructural organization that enables cells to move and carry out receptor-mediated endocytosis, phagocytosis, pinocytosis, and mitosis and on the influence of extracellular matrix on cell structure and function.

- Ultrastructural Cytochemistry Section—
  Mark Willingham, M.D.

This section focuses on the study of basic cellular mechanisms of cell and organelle movement and function using morphologic techniques, especially electron and light microscopic immunocytochemistry, image intensification microscopy of living cells, and direct microinjection of single cells in tissue culture.

- Membrane Biochemistry Section—
  Kenneth Yamada, M.D., Ph.D.

The structure and function of plasma membrane and extracellular glycoproteins such as fibronectin are examined by biochemical, immunological, and cell biological approaches using normal and malignant cells.

- Developmental Genetics Section—
  Sankar Adhya, Ph.D.

To elucidate the mechanisms of control of gene expression in prokaryotes, genetic and biochemical experiments are conducted to determine how various regulatory molecules function to modulate transcription and/or translation.

- Molecular Cell Genetics Section—
  Michael Gottesman, M.D.

Molecular and somatic cell genetic approaches are used to analyze malignant transformation, growth control, cytoarchitecture, and drug resistance of cultured cells. Techniques employed include mutant isolation, somatic cell hybridization, gene transfer, and molecular cloning.

- Molecular Genetics Section—
  Bruce Howard, M.D.

Research focuses on development and application of techniques for introducing genetic material into mammalian cells. Emphasis is placed on isolation of genes that control cell growth, with the goal of understanding how abnormal expression of such genes may contribute to malignant transformation and cellular senescence.

Laboratory of Pathology—
Lance A. Liotta, M.D., Ph.D.

- Surgical Pathology and Postmortem Section—Ernest E. Lack, M.D.
- Hematopathology Section—
  Elaine S. Jaffe, M.D.
- Cytopathology Section—
  Elizabeth W. Chu, M.D.
- Tumor Invasion and Metastases Section—
  Lance A. Liotta, M.D., Ph.D.
- Biochemical Pathology Section—
  David A. Zopf, M.D.
- Ultrastructural Pathology Section—
  Timothy J. Triche, M.D., Ph.D.
- Viral Oncology and Molecular Pathology Section—
  Peter M. Howley, M.D.
- Image Processing Section—
  Lewis E. Lipkin, M.D.
- Pathological Technology Section—
  Barbara Coolidge

The Laboratory of Pathology of the National Cancer Institute offers a 2- to 3-year training program for residents in pathologic anatomy. This program, which is fully approved for Board certification, provides well-supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology, and neuropathology can be arranged. The research activities of the staff are varied, and participation in clinical or basic research projects is an intrinsic part of the program during elective periods. Research interests of the laboratory include: viral oncology, molecular biology, immunopathology, immunochemistry, mechanisms of metastasis, comparative oncology, and tumor biology.

In addition, the laboratory offers research training in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies of viruses and neoplastic cells.

Laboratory of Pathophysiology—
Pietro M. Gullino, M.D.

A group of projects concerning the mammary gland is carried on in connection with the Office of the Chief. Richard Knazek, M.D., Ph.D., studies the mechanism of prolactin action and role of prostaglandins on hormone receptor development. Barbara Vonderhaar, Ph.D., evaluates the role of thyroid hormone-prolactin interactions on mammary gland development and tumorigenesis. Pradman Qasba, Ph.D., using recombinant DNA technology, is studying the expression of differentiated functions during growth and regression of normal and neoplastic mammary glands, and P.M. Gullino, M.D., works on the mechanism and prognostic value of angiogenesis in neoplastic and preneoplastic tissues.

- Section on Cell Cycle Regulation—
  William Kidwell, Ph.D.

Laboratory investigations are concerned with characterization of biologic events uniquely required for the cell to progress through S, G_2, M, G, and G_0 phases. Emphasis is placed on the nutritional, hormonal and other factors involved in initiation of cellular transition through division to a differentiated state and the interrelationship among various organ cell types in this progressive change. Specific studies relate to the interaction of epithelial, myoepithelial, and stromal cells, and adipocytes in the proliferative response of the mammary gland to hormones.

- Section on Cellular Biochemistry—
  Yoon Sang Cho-Chung, M.D., Ph.D.

This section studies the mechanisms controlling cell growth and regression. Emphasis is placed on the roles of cyclic nucleotides, hormones, and other intracellular mediators in the growth control of normal and neoplastic cells. Current studies involve the mechanism of action of cyclic nucleotides in the regression of mammary tumors and suppression of mammary carcinogenesis.

- Section on Membrane Biology—
  Pedro Pinto da Silva, Ph.D.

This section investigates the structure and dynamics of biological membranes, using freeze-fracture and freeze-etch electron microscopy alone or in combination with cytochemical labeling techniques.

Laboratory of Mathematical Biology
Charles DeLisi, Ph.D.

- Membrane Structure and Function—
  Robert P. Blumenthal, Ph.D.

This section investigates the dynamics of membrane components (lipids, proteins) in biological membranes and in reconstituted lipid-protein systems using a variety of biophysical techniques. Current studies examine how proteins are inserted into membranes, how membranes fuse, and how given membrane components are maintained in specific domains such as apical and basolateral surfaces in epithelial cells.

- Theoretical Immunology—
  Charles DeLisi, Ph.D.

Research areas include the following: theories of receptor function and physical chemistry, with emphasis on the analysis of data bearing on exocytosis, endocytosis, and chemotaxis, and development of statistical methods for predicting function, location and structure of protein sequence. Current applications are to oncogene products and/or gene products.

- Molecular Structure, Properties, and
  Function—Robert L. Jernigan, Ph.D.

Biopolymers and their conformations and properties are investigated from a theoretical viewpoint. Studies of proteins include enumerations of favorable pathways for achieving native protein conformations. The basic research consists primarily of developing new methods to treat such problems of current interest in molecular biology. Applications, which are typically computer intensive, include globular proteins, membrane proteins, structural proteins, and DNA translation products. DNA flexibility and its origin and effect on physical properties is another area of interest.

- Immunopharmacology—
  John N. Weinstein, M.D., Ph.D.

Monoclonal antibodies (and their conjugates with toxins, radionuclides, and liposomes) are investigated for diagnosis and treatment of cancer. The approach is eclectic, involving membrane biophysics and biochemistry, immunochemistry, *in vitro* cell studies, *in vivo* animal pharmacology, and theoretical modeling. Current emphasis is on delivery to lymphoma and metastases in lymph nodes.

Laboratory of Genetics—
Michael Potter, M.D.

Much of the focus of research is on the role of genes that determine susceptibility and resistance to neoplastic development and special genes and their products that are associated with the neoplastic state (oncogenes, retroviral gene products, tumor associated antigens). The laboratory has had a long association with the study of the plasma cell tumor system in mice. Research continues on the organization of immunoglobulin genes, and gene families and structure function correlations with monoclonal antibodies.

Current ongoing projects concern: expression of the myc (and other) oncogenes in lymphomas and plasmacytomas; immunoglobulin V_K and V_H gene families in the genus *Mus*; structure and identification of contact amino acids in phosphorylcholine; lysozyme and galactan binding monoclonal antibodies; pathogenesis of erythroleukemia in mice; thyroglobulin producing cell lines; isolation and characterization of unique tumor associated antigens; and the search for genes that control susceptibility to plasmacytomagenesis in BALB/c mice.

The laboratory can provide research training in amino acid and DNA sequences, recombinant DNA technology, tissue culture, hybridoma-monoclonal and antibody production.

Laboratory of Tumor Immunology and Biology—
Jeffrey Schlom, Ph.D.

The laboratory conducts research to identify immunologic markers specific for, or associated with, various human neoplasms, with the ultimate aim of applying these toward the diagnosis, prognosis, and treatment of human cancer. Specifically, the laboratory is engaged in studies involving the generation and characterization of monoclonal antibodies to tumor associated determinants with particular emphasis on the study of human carcinomas. Studies ongoing involve the conjugation of monoclonal antibodies to isotopes or toxins, to aid in the diagnosis, localization, and potentially the elimination of tumor cells. Immunoassays are being developed that will aid in the characterization of human tumor cell populations, and in the diagnosis or prognosis of certain human cancers. The laboratory is also engaged in studies to investigate the association between specific murine and human genetic elements and tumorigenesis, employing techniques of gene cloning and molecular hybridization.

- Experimental Oncology Section—
  Jeffrey Schlom, Ph.D.

Projects underway include research to generate and characterize monoclonal antibodies that are reactive with mammalian carcinoma cells with emphasis on human breast and colon carcinomas; to use monoclonal antibodies to identify and characterize specific proteins that are associated with the neoplastic state, with emphasis on human carcinoma systems; and to develop immunoassays that will aid in the characterization of human carcinoma cell populations and in the diagnosis or prognosis of human carcinomas. The use of monoclonal antibody, conjugated with isotopes, is being investigated to aid in the detection or therapy of carcinoma lesions. Experiments are being conducted to determine those factors which influence the antigenic modulation, antigenic phenotype, and the state of differentiation of human carcinoma cell populations.

- Oncogenetics Section—
  Robert Callahan, Ph.D.

This section seeks to identify and molecularly clone tumor specific cellular and viral genetic elements from human carcinoma and other mammalian tumors. Research is being conducted to determine the organization of tumor specfic genetic elements in cellular DNA, and the biological activity and the role of tumor specific genes in normal and neoplastic tissue. The ultimate aim is to develop an understanding of the genetic changes which are relevant to the etiology of human neoplasia.

- Biochemistry of Oncogenes Section—
  Robert Bassin, Ph.D.

Investigations of the mechanisms of cellular transformation mediated by RNA tumor viruses and by related cellular oncogenes are under way, em- phasizing the nature and functions of specific cellular proteins which are involved in the transformation process. Studies are being conducted to identify genetic elements responsible for tumorigenesis and for immunologic markers specific for various human carcinomas. Studies are also being carried out to investigate the cellular control mechanisms which are active in preventing infection and disease by endogenous RNA tumor viruses.

- Molecular Control and Genetics Section—
  Donald L. Court, Ph.D.

This section conducts research in prokaryotic and eukaryotic molecular biology; employs recombinant DNA techniques and molecular genetics to study the mechanism of genetic recombination and to specify the role that recombination plays in the expression of viral and cellular genes; uses recombinant DNA techniques and molecular genetics to study the effect of genomic recombination on the expression of isolated viral and cellular genes; and examines the expression and mode of chromosomal association in eukaryotic hosts of specific eukaryotic genes which are recombined in prokaryotic host-vector systems.

Division of Cancer Etiology, NCI

Richard H. Adamson, Ph.D., Director

The Division of Cancer Etiology plans and directs laboratory, field and epidemiologic and biometric research on the cause and history of cancer. It studies prevention of cancer through direct intramural research, research grants and contracts; evaluates mechanisms of cancer induction and promotion by chemicals, viruses and environmental agents; serves as the focal point for the federal government on the synthesis of clinical, epidemiological, and experimental data relating to cancer causation; and advises the Institute Director on basic research activities as they relate to cancer cause and prevention.

Carcinogenesis Intramural Program—
Richard H. Adamson, Ph.D.
Acting Associate Director

The Carcinogenesis Intramural Program conducts a basic laboratory research program on the causes of cancer by chemical, physical, and biological (viral) factors; and on the pathogenesis and prevention of various cancers.

Laboratory of Biology—
Joseph A. DiPaolo, Ph.D.

The Laboratory of Biology is primarily interested in the modulation of the transformation process that leads to malignancy. The primary objective is to determine the crucial molecular and physiological changes that occur in cells which have been treated with chemical or physical agents as they transform from the normal to the neoplastic state. The laboratory uses biological preparations, cells from animals and humans and a variety of intact mammals. The present emphasis is the study of oncogenes and DNA changes which are responsible for the activation of genes in neoplasia. Concurrently, the role of growth factors, in particular, lymphotoxin, a hormone which is noncytotoxic to normal cells and is capable of inhibiting the transformation process, is being investigated in terms of its cell receptor and interaction with other physiological agents during carcinogenesis.

Laboratory of Carcinogen Metabolism
Snorri S. Thorgeirsson, M.D., Ph.D.

The Laboratory of Carcinogen Metabolism conducts investigations on malignant transformation in human and animal cells by chemical carcinogens and other cancer causing agents; investigations on the mechanism of the regulation of gene expression by hormones and growth factors; defining the cellular events which mediate the conversion of normal cells into neoplastic or cancer cells; and studies on the chemical structure and conformational aspects of relevant biopolymers, chemical carcinogens and of carcinogen-biopolymer adducts using rigorous spectral and chemical methods.

Laboratory of Cellular and Molecular Biology—
Stuart A. Aaronson, M.D.

The program of the Laboratory of Cellular and Molecular Biology is primarily focused on defining the factors contributing to oncogenesis at the molecular level. Major emphases are on the molecular mechanisms involved in RNA tumor virus-induced cancers and isolation and characterization of human oncogenes. Techniques employed include gel electrophoresis, restriction enzyme analysis, Southern blotting technique, electron microscopy, immunology, genetics, and tissue culture. Materials utilized in studies include animal retroviruses including transforming sarcoma viruses, normal fibroblasts and epithelium from genetically compromised individuals at high risk for cancer and cells derived from human and animal cancers. Disciplines represented within the laboratory include virology, immunology, biochemistry, cell biology, and molecular genetics. Ongoing collaborations include, in addition to the above, oncology and epidemiology.

Laboratory of Cellular Carcinogenesis and Tumor Promotion—
Stuart Yuspa, M.D.

The Laboratory of Cellular Carcinogenesis and Tumor Promotion plans, develops and implements a comprehensive research program to determine the molecular and biological changes which occur at the cellular and tissue levels during the process of carcinogenesis. Studies are designed to define normal regulatory mechanisms for cellular growth and differentiation; determine the mechanism by which carcinogens alter normal regulation and the biological nature of these alterations; investigate the mechanism by which tumor promoters enhance the expression of carcinogen-induced alterations; identify cellular determinants for enhanced susceptibility or resistance to carcinogens and tumor promoters; and elucidate the mechanism by which certain pharmacologic agents inhibit carcinogenesis.

The laboratory is composed of three sections, each of which is charged with a major responsibility for portions of the laboratory goals. Because of the integrated approach toward an understanding of mechanisms of carcinogenesis, considerable interaction occurs among the sections.

- The *In Vitro* Pathogenesis Section—
  Stuart Yuspa, M.D.

This section develops relevant model systems for the study of all phases of the process of carcinogenesis; defines regulatory mechanisms for the normal control of growth and differentiation and alterations in these controls induced by initiators and promoters; produces, isolates and studies initiated cells; studies functional alterations in gene expression produced by initiators and promoters and the mechanism by which these functional changes occur; and elucidates factors which determine susceptibility to carcinogenesis.

- The Differentiation Control Section—
  Luigi DeLuca, Ph.D.

This section studies the biological and biochemical factors involved in normal differentiation of epithelial tissues; uses pharmacological techniques to alter differentiation of normal, preneoplastic and neoplasteic epithelial cells to determine the relevance of differentiation to carcinogenesis and to determine methods to intervene in preneoplastic progression; studies the relationship between differentiation and growth control; and focuses on cell surface changes in differentiation and neoplasia.

- The Molecular Mechanisms of Tumor Promotion Section—
  Peter Blumberg, Ph.D.

This section studies the interaction of promoters with specific cellular receptors; elucidates the functional importance of receptors in promoter action; identifies endogenous ligands with specific affinity for receptors of exogenous promoters; and characterizes the initial biochemical steps in the cascades associated with receptor occupancy. In approaching these goals, the laboratory utilizes the latest technology in cell and molecular biology, as well as biochemical, pharmacological and immunological methods.

Laboratory of Experimental Pathology—
Umberto Saffiotti, M.D.

This laboratory focuses on the study of neoplastic transformation and its underlying mechanisms, with particular emphasis on epithelial target cells. It plans, develops and implements research on the experimental pathology of carcinogenesis, especially concerned with the induction of neoplasia by chemical and physical factors in epithelial tissues, including: development, characterization and evaluation of experimental pathology models of human cancer, such as cancers of the respiratory tract, by *in vivo* and *in vitro* carcinogenesis methods; development and characterization of tissue culture systems for quantitative study of the effects of carcinogens alone or in combination; and research on mechanisms of carcinogenesis correlating different levels of biological organization, from whole organisms (human and animal), organs and tissue, to the cellular, subcellular and molecular levels.

Chemical carcinogenesis mechanisms are studied in various cellular model systems. Quantitative relationships are investigated for different end-points such as cytotoxicity, DNA repair, mutation and transformation. DNA-mediated gene transfer is used to identify the diversity of transforming genes activated by chemical carcinogens and co-factors. Molecular biology studies are addressed to the characterization of new transforming genes and to the investigation of DNA regions that may have particular specificity for interacting with carcinogens. Metabolism and interactions are studied for several known or suspected carcinogens. Other studies related to transformation mechanisms include the role of cell membrane associated phosphoproteins and modifications in bioenergetic pathways.

- Respiratory Carcinogenesis Section—
  Umberto Saffiotti, M.D.

In vivo studies of multifactorial carcinogenesis in the respiratory tract by organic and inorganic chemicals, particulate materials and physical factors are paralleled by studies on the underlying cellular mechanisms of cell proliferation and differentiation, and by studies of the cells of origin of tumors *in vivo* and in culture.

- Tissue Culture Section—
  M.E. Kaigh, Ph.D.

Chemically defined, serum-free culture methods are developed to provide optimal conditions for growth, differentiation and neoplastic transformation of epithelial cell systems; current studies are on mouse epidermal, hamster respiratory and human bladder epithelial cells. Mechanisms involved in the control of cell differentiation and transformation are investigated in collaboration with other parts of the laboratory.

Laboratory of Human Carcinogenesis—Curtis C. Harris, M.D.

The Laboratory of Human Carcinogenesis conducts investigations to assess (a) mechanisms of carcinogenesis in epithelial cells from humans and experimental animals, (b) experimental approaches in biological systems for the extrapolation of carcinogenesis data and mechanisms from experimental animals to the human situation, and (c) host factors that determine differences in carcinogenic susceptibility among individuals.

Medical staff fellows spend 2 to 3 years in the laboratory investigating problems in three areas (examples of studies are also listed):

Molecular and Biochemical Epidemiology—Measurement of gene polymorphism by molecular approaches, e.g., DNA polymorphism, to identify host susceptibility factors that predispose to cancer; measurement of carcinogen-DNA adducts and other carcinogen-induced lesions in biological samples from individuals in environments associated with high and low risk for cancer; and studies of interactions between the effects of cocarcinogens and carcinogens.

Carcinogen Macromolecular Interaction—Activation of cellular oncogenes by carcinogens; identification of metabolic pathways of carcinogen activation and deactivation; inter- and intragenic damage and rearrangements caused by chemical and physical carcinogens; and determination of the importance of repair of carcinogen-induced damage to DNA and chromosomes in carcinogenesis.

In Vitro Carcinogenesis—Investigation of the mechanisms of neoplastic transformation; role of oncogene expression in human cell carcinogenesis; studies of phenotypic and genetic alterations during *in vitro* carcinogenesis; assessment of the relationship between carcinogenesis, mutagenesis, and differentiation in mammalian cells; and identification of extra-, inter- and intra-cellular factors modulating growth and differentiation of human epithelial cells.

Medical staff fellows may also participate in combined laboratory-epidemiology studies and are encouraged to collaborate with epidemiologists.

Laboratory of Molecular Carcinogenesis
Harry V. Gelboin, Ph.D.

The goal of the Laboratory of Molecular Carcinogenesis is an increased understanding of the cellular and biochemical events and mechanisms involved in carcinogenesis: a study of various aspects of initiation and promotion by chemicals in tissue culture, with emphasis on mutation and the consequences of altered cellular proteins, especially actin. DNA transfection and sequencing are used to define the genomic changes observed; examination of the unusual properties of cells from patients who may be predisposed to cancer because of hereditary disease, and an investigation of various mechanisms of DNA repair. Emphasis is placed on DNA repair properties of malignant human cells; investigation of the genetics, multiplicity, and structure of the drug and carcinogen metabolizing enzyme systems. Monoclonal antibodies are used to gain an understanding of individual differences and their relationship to drug and carcinogen sensitivity; shuttle vectors which replicate in mammalian and bacterial cells are used to study the mutation, recombination, and repair caused by carcinogen treatment. Genetic stability of the genome under various circumstances is evaluated by DNA sequencing; a study on the temporal control of events in the cell-cycle of normal and malignant cells. Synchronized cell populations are used; and a study of the relationship between structure and function in chromatin, using biochemical and immunological methods, including evaluation of the regulatory properties of the non-histone proteins.

Laboratory of Molecular Oncology
Takis S. Papas, Ph.D. Acting

This section plans and conducts research on the molecular elements responsible for the development and expression of malignant phenotypes in humans and animals; and applies skills in molecular biology, recombinant DNA technology and hybridoma-monoclonal antibody production in a comprehensive program to identify and isolate cellular transforming genes and to characterize products expressed by these genes.

- Tumor Biochemistry Section—
  Takis S. Papas, Ph.D., Acting

This section investigates the molecular elements essential for cellular transformation; isolates specific regions of viral and cellular transforming phenotypes by recombinant DNA techniques; and determines structural properties of the cloned fragments and their transforming activities as characterized by biological assays.

- Microbiology Section—
  Donald G. Blair, Ph.D.

This section is concerned with the biological analysis of oncogenes in human and non-human genomes, and in the development of biological assays using animal models and tissue culture techniques to detect and isolate such genes and to determine the factors necessary for them to cause neoplastic transformation and tumor growth.

- Carcinogenesis Regulation Section—
  Takis S. Papas, Ph.D.

This section studies the relationship between oncogenic viral gene expression and the conversion of cells from normal to transformed phenotype; and tests specific regions of molecular cloned acute transforming retroviruses for transforming activity and elucidates the molecular mechanisms of interaction with the cell.

- Cellular Transformation Section—
  John P. Bader, Ph.D.

This section identifies virus-coded protein responsible for the malignant transformation of cells by Rous sarcoma virus; determines the biochemical function of this protein; determines the primary physiological effects resulting from the functioning of this protein; describes the sequence of metabolic changes which result in the altered metabolic profile characteristic of malignant cells; and distinguishes metabolic changes necessary for the maintenance of the malignant state.

- **Laboratory of Molecular Virology—**
  George Khoury, M.D.

This laboratory is interested in the normal and abnormal regulation of gene expression. Specific studies employ methods from molecular biology, immunology, virology and cell biology in an attempt to determine in specific cases what signals regulate gene expression. Presently the laboratory is interested in both viral and eukaryotic genetic units. The research efforts are focused on genes which are regulated at the level of transcription and which, in some cases, are responsive to induction by hormones or other stimuli. The laboratory has made a commitment to the study of oncogenes and the mutations which are responsible for the activation of these genes in neoplasia. Studies are being pursued on the histocompatibility antigens in hopes of determining the role of these genes in immune surveillance and tumor immunity.

- **Laboratory of Viral Carcinogenesis—**
  Stephen O'Brien, Ph.D., Acting

This laboratory is committed to basic research approaches to unravelling the genetic and cellular mechanism of neoplastic transformation in man and in mammalian model systems. Studies are conducted on the specific cellular genes which participate in transformation from several distinct approaches. Endogenous mammalian retroviruses are studied in attempts to understand their role in gene regulation and in neoplasia. Transforming viruses, their included oncogenes and their ancestral cellular homologues are being examined using recombinant DNA technologies and systems for studying their expression during development and during carcinogenesis. Processes of chemical carcinogenesis are studied using gene cloning, cell transfection and cell biology procedures. Chromosomal gene mapping of loci related to both chemical and viral transformation is an important component of the laboratory as are the cytogenetic consequences of transformation. The laboratory is also studying the nature of hormone-like tumor-growth factors, tumor-inhibitory factors, and tumor promoters to determine their relationship to malignant genes and to the progressive stages of transformation of cells *in vitro* and *in vivo*. Since some classes of these factors clearly accelerate transformation or inhibit or reverse the process, they present attractive opportunities to explore further research and clinical applications.

Epidemiology and Biostatistics Program—
Joseph F. Fraumeni, Jr., M.D.
Associate Director

Medical staff fellow positions are available for 2-year assignments in the three branches of the Epidemiology and Biostatistics Program, which provides the focus for epidemiologic and biostatistical research within the Institute. The program conducts epidemiologic investigations into the environmental and host determinants of human cancer; analyzes the natural history of cancer and the efficacy of therapeutic and preventive measures; and designs statistical models for clinical and experimental investigations.

Environmental Epidemiology Branch—
Robert N. Hoover, M.D.

The Environmental Epidemiology Branch conducts a wide range of studies to clarify the risk of cancer among persons exposed to occupational, nutritional, medicinal, radiogenic, infectious or other environmental hazards, and among persons with genetic or immunologic predisposition. Multidisciplinary studies with laboratory scientists are carried out whenever feasible.

Clinical Epidemiology Branch—
Robert W. Miller, M.D.

The Clinical Epidemiology Branch investigates the origins of human cancer by starting from peculiarities of cancer occurrence recognized at the bedside and studied through the disciplines of clinical medicine, epidemiology, and cellular genetics and other laboratory sciences. Current emphasis is given to the clinical delineation of cancer family syndromes and disorders that predispose to cancer, such as neurofibromatosis and certain birth defects, and to studies evaluating the late effects of cancer treatments, including reproductive toxicity. Liaison is maintained with many clinical services throughout the Washington area and beyond, as well as with the NIH Interinstitute Medical Genetics Program. Physicians selecting this Branch need not have specific training in epidemiology or genetics, and may become Board-eligible in medical genetics through the NIH Interinstitute Medical Genetics Program.

Radiation Epidemiology Branch—
John D. Boice, Jr., Sc.D.

This branch conducts studies to identify and quantify the risk of cancer in populations exposed to ionizing radiation, especially at low-dose levels. These include patient populations given diagnostic or therapeutic radiation alone or in combination with cytotoxic drugs and other forms of treatment.

Biostatistics Branch—
Joseph F. Fraumeni, Jr., M.D. (Acting)

The Biostatistics Branch uses biometric and mathematical approaches to investigate the distribution, causes and natural history of cancer. New statistical methods are developed for designing and analyzing epidemiologic, clinical, and experimental studies of cancer. Mathematical models are explored to clarify processes of cancer biology and carcinogenesis, and improve methods of quantitative cancer risk assessment.

Division of Cancer Treatment

Bruce A. Chabner, M.D., Director

This Division carries out a broad program of basic and clinical research concerning the treatment of cancer. The major areas of research are radiation therapy, drug therapy, modifiers of tumor growth and differentiation, and surgical approaches to cancer treatment. Treatment programs are multidisciplinary in nature, involving the cooperative efforts of medical, surgical, and radiotherapy staff members.

Cancer Therapy Evaluation Program—

Daniel Hoth, M.D., Acting Associate Director

One medical staff fellow position is open each year within the Cancer Therapy Evaluation Program. The fellow is assigned to the Investigational Drug Branch for 1 year. Subsequently, a second year program may be developed in conjunction with other branches or laboratories within the Division of Cancer Treatment, or within the Cancer Therapy Evaluation Program by rotating to the Clinical Investigations Branch. It is anticipated that the second-year medical staff fellow will also maintain some responsibility for drug monitoring. Eligibility for a third year within the program is feasible. The duties within the Investigational Drug Branch include developing and coordinating clinical research efforts on specific new antineoplastic drugs developed by the NCI. Special projects in the area of antineoplastic drugs are available. The work within the Clinical Investigations Branch includes monitoring research and progress in grant and cooperative agreement programs, reviewing new research protocols, developing new research strategies along disease or modality lines, providing overviews of research topics, and planning discussion groups and intergroup studies.

The major function of the Cancer Therapy Evaluation Program is to sponsor clinical trials of investigational and known antineoplastic treatment modalities and to monitor those trials with investigational chemotherapeutic agents to a disease-oriented approach. This includes the incorporation of effective chemotherapeutic combinations in early stages of disease and testing of new modalities, such as immunotherapy in combination with surgery, radiotherapy, and chemotherapy in specific disease entities until now considered untreatable. For these purposes, the program has planned and helped organize several study groups designed to test combined modality approaches to specific diseases. The program also supports, through the cooperative agreement mechanism, various clinical cooperative groups made up of institutions of higher education. These cooperative groups share in the design, development, execution, and analysis of clinical protocols. The program encourages and sponsors disease-oriented meetings with representatives from all interested groups to achieve coordination of clinical research efforts at a national level. Staff members of the program periodically attend meetings of the clinical cooperative groups, disease-oriented task forces, and working parties. In addition, the program serves as a vehicle of communication between inhouse preclinical and clinical programs and extramural activities.

The program coordinates clinical conferences sponsored by the chemotherapy area, which is an important mechanism for informing clinical investigators throughout the world on the status of drug trials. The conferences are held to discuss the clinical programs concerned with drug development. The program also maintains a special relationship with the Clinical Oncology Program's branches, the Biological Response Modifiers

Program, and the Radiation Research Program. In addition, it is responsible for the development of new areas of clinical research and dissemination of information on clinical trials to investigators in foreign countries, and is responsible for receiving and analyzing information from abroad.

Clinical Investigations Branch—
Edwin Jacobs, M.D., Acting

The Clinical Investigations Branch monitors and coordinates a broad range of research activities. This includes research support for individual investigator-initiated projects (R01), program project grants (P01), cooperative group agreements (M10), and planning grants (P20). This research spans the spectrum from laboratory research to Phase III clinical trials. Staff responsibilities include critical review and participation in the development of protocols developed by cooperative groups and intergroup studies. Staff members also develop overviews of research progress, formulate strategies for future research directions, and plan discussion groups on selected topics. There is a major emphasis on integration of modalities in the treatment of cancer.

This branch also maintains liaison with international clinical research groups and the Breast Cancer Task Force.

- Medicine Section—
  John Y. Killen, Jr., M.D.

This section reviews, monitors, and coordinates studies related to medical oncology and hematology, including studies of supportive care, basic investigations, and clinical trials. Members evaluate and stimulate research in chemotherapy (Phase II and III) and in the design of comprehensive therapeutic programs aimed at improving response to therapy and increasing the cure rate for specific neoplastic diseases.

- Nutrition Section—
  Edwin Jacobs, M.D., Acting

This section plans, develops, evaluates, and administers grant- and cooperative agreement-supported research concerning the role of nutrition in the care and treatment of cancer patients. Areas of interest include the mechanisms of nutritional derangement in cancer patients, the prognostic effect of altered nutritional status, the application of basic nutritional research to the cancer patient, and the development of innovative approaches to the nutritional management of cancer patients.

- Pediatric Section—
  Richard Ungerleider, M.D.

This section is responsible for review, evaluation, and stimulation of multimodal approaches to the treatment of childhood malignancies. This includes development and monitoring of phase I-II clinical trials in pediatric malignancies, liaison with investigators at cancer centers treating childhood malignancy, and monitoring and interacting with investigators in the Clinical Cooperative Groups involved in pediatric cancer.

- Surgery Section—
  Ernest DeMoss, M.D.

This section plans, evaluates, and administers grant-supported research concerning the role of surgery in the care and treatment of cancer patients. Topic areas of interest include evaluation of new or modified surgical techniques; development of techniques for vascular infusion, perfusion, and occlusion; tumor immunology; biology of metastases; staging procedures; and evaluation of prognostic factors in the surgical treatment of cancer patients.

Investigational Drug Branch—
Silvia Marsoni, M.D., Acting

This branch monitors and coordinates the drug-oriented trials of the Division. The branch serves as a link between the preclinical and clinical aspects of the drug development part of the Division with special interest in the pharmacologic investigations of new drugs. Interaction with investigators is a vital part of the work of the branch in providing supervision, advice, and retrieving information on therapeutic response and toxicity.

- Regulatory Affairs Section—
  Daniel Hoth, M.D., Acting

The section provides liaison with the Food and Drug Administration and supervises the preparation of all FDA filings on new drugs. This involves a close working relationship with intramural branches and committees dealing with submission of data to meet regulatory requirements.

- Drug Evaluation and Reporting Section—Silvia Marsoni, M.D.

The section reviews, coordinates, and monitors protocol studies for Phase I and early Phase II clinical trials supported under contract. The section prepares annual reports on IND drug studies and investigates and reports on Adverse Drug Reactions.

- Drug Management and Authorization Section—Clarence Fortner, M.S.

This section authorizes the distribution of NCI-sponsored investigational new drug agents to eligible investigators and administers the program of accountability for the use of investigational drugs distributed under NCI sponsorship. It assures that the FDA regulatory requirements for the distribution of investigational agents are met.

- Biologics Evaluation Section—Luz Hammershaimb, M.D., Acting

This section develops plans for Phase II and III trials with biological response modifiers and interacts with investigators and the pharmaceutical industry in designing these trials. It monitors the clinical trials of biological agents sponsored by NCI and provides annual reports to the FDA.

- Quality Assurance Compliance Section—Daniel Hoth, M.D., Acting

The responsibility of this section includes managing the site-visit monitoring program for all clinical trials using NCI-sponsored agents, coordinates all monitoring activities within the clinical cooperative groups, and provides information to all NCI clinical investigators regarding FDA regulations, NCI policies, procedures, and human subjects regulations.

Radiotherapy Development Branch—
David A. Pistenmaa, M.D., Acting

The Radiation Research Program (RRP) was established in May 1982 and consists of the Diagnostic Imaging Research Branch, the Low-Level Radiation Effects Branch, and the Radiotherapy Development Branch. The program is responsible for the support of extramural preclinical and clinical research in imaging therapy with ionizing and non-ionizing radiations as well as the biological and health effects of ionizing and nonionizing radiations. The RRP has no intramural research component. Thus, someone who chooses to spend time in the RRP would be involved primarily with the planning, management, and evaluation of those aspects of the $60 million grant- and contract-supported research program in which he or she has interest. This experience might be especially valuable for someone interested in academic medicine who would be expected to seek grant or contract support for research in later years.

Clinical Oncology Program—
Samuel Broder, M.D.
Associate Director

The Clinical Oncology Program (COP) recruits approximately 18 medical staff fellows each year for a 3-year assignment in medical oncology or a 2-year assignment in surgical oncology. Fellows are recruited for one of the following clinical branches: Medicine, Pediatric Oncology, Radiation Oncology, and Surgery, located in the NIH Clinical Center on the Bethesda campus, or NCI-Navy Medical Oncology Branch located at the National Naval Medical Center, Bethesda, Maryland. The program also offers a residency training program in radiotherapy.

The 3-year medical oncology training program is offered to candidates who have at least 2 years of postgraduate training (internship and first-year residency) in medicine or pediatrics. The first year consists of primary responsibility for the clinical care of both inpatients and outpatients. The staff fellow may sometimes take a full year with a single clinical service, or take two 6-month rotations through the clinical services of the COP. The second and third years consist of clinical and/or laboratory research under the supervision of a member of the senior staff. Medical staff fellows will have the opportunity to select a project from the numerous current studies in the laboratories of the Clinical Oncology Program, the Developmental Therapeutics Program, or the Biological Response Modifiers Program. Opportunities are also available for clinical trial monitoring in the Cancer Therapy Evaluation Program. Clinical electives are available on consultative services in the branches and other related departments, and in various procedures, such as peritoneoscopy. Second- and third-year medical staff fellows continue to follow patients in the Outpatient Department. Offered throughout the program are lectures, clinical conferences, research seminars, teaching rounds, and joint conferences relevant to the field of clinical oncology and cancer research. Certain clinical conferences are mandatory.

Candidates otherwise qualified who successfully complete the program are eligible for Board certification in the subspecialty of medical oncology or pediatric hematology-oncology.

For further information, applicants to the medical or pediatric oncology training programs should write to:
Associate Director
Clinical Oncology Program
National Cancer Institute,
Building 10, Room 6B15
Bethesda, MD 20205.

The Surgery Branch offers a 2-year surgical oncology training program. This program consists of a 6-month period on the wards of the Surgery Branch, inpatient and outpatient services, and 1½ years in one of the laboratories of the senior staff in the Surgery Branch. Selected medical staff fellows may remain for a third year to continue their laboratory research. Applicants interested in the Surgery Branch program should write director Steven Rosenberg, M.D., Ph.D., Surgery Branch, Building 10, Room 10N116, National Cancer Institute, Bethesda, MD 20205.

Applicants interested in the radiotherapy residency should write to Eli Glatstein, M.D., Radiation Oncology Branch, Building 10, Room B3B69, National Cancer Institute, Bethesda, MD 20205.

Clinical Pharmacology Branch—
Charles Myers, M.D.

This group conducts laboratory and clinical research activities on problems of drug action and toxicity in man and, as such, plays a supporting role for the chemotherapy programs of the other clinical branches of the NCI. The branch does not have patient care responsibilities of its own, but accomplishes its clinical studies through collaborative ties with the other clinical branches. Research training opportunities are available for physicians completing 1 year of clinical training in the Clinical Oncology Program or for trainees of the Clinical Pharmacology Training Program of the National Institute of General Medical Sciences.

Areas of specific research interest include: mechanisms of adriamycin cytotoxicity; mechanism of action and cellular pharmacology of antimetabolites; pharmacokinetics and metabolism of established and new antineoplastic agents; clinical and experimental applications of cytofluorometry; and molecular genetics of drug resistance.

Medicine Branch—
Robert C. Young, M.D.

The Medicine Branch is an adult medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of the malignant lymphomas, Hodgkin's disease, breast cancer, ovarian carcinoma, sarcomas, melanoma, endometrial cancer, chronic leukemias, and testicular cancer. Training in clinical diagnostic procedures such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH, such as cancer surgery and radiation therapy. The

Branch has an active autologous marrow infusion program.

The branch conducts weekly clinical conferences with the departments of radiation oncology, pathology, clinical pathology (hematology), and radiology on current problems and on the staging of lymphomas, Hodgkin's disease, and testicular carcinoma. Research focuses on the general areas of kinetics and cytogenetics of neoplastic and hemopoietic cells, immunological alterations induced by disease or chemotherapy, and the biochemical pharmacology of antineoplastic agents. In addition, an active research program is under way in the field of hormone receptors, tumor markers, and tissue culture. The branch conducts weekly laboratory conferences, in conjunction with the Clinical Pharmacology Branch, on laboratory topics of mutual interest. Collaboration with the Clinical Pharmacology Branch and other laboratory groups is maintained.

NCI-Navy Medical Oncology Branch—
John D. Minna, M.D.

The NCI-Navy Medical Oncology Branch is located at the National Naval Medical Center (NNMC) in Bethesda, Maryland across the street from the NIH Clinical Center. This branch is part of the NCI intramural Clinical Oncology Program and, with the Navy Hematology-Oncology Branch (Steven Veach, M.D., Chief), part of the NNMC cancer treatment program. The NNMC is a 450 bed tertiary referral hospital for active duty military, military retired, and military dependents. Patients are referred from around the world with all types of malignant diseases including solid tumors (e.g. lung, breast, gastrointestinal) and hematologic malignancies (Hodgkin's disease, non-Hodgkin's lymphomas, and acute and chronic leukemias). There is a large population of young adults with such malignant diseases as germ cell tumors. The program has a 20-bed inpatient service, and also provides consultation in oncology and hematology to the NNMC (approximately 40-60 active inpatients at any one time). In addition, civilian patients who are eligible for certain NCI studies can be admitted to the program for care and study. The NCI-Navy Medical Oncology and Navy Hematology-Oncology Branches represent a joint and integrated NCI-Navy effort in cancer patient care, clinical and laboratory investigation, and training in clinical oncology and hematology. More than 1,000 patients are followed by the NCI-Navy Program in a study and primary care setting and each fellow has approximately 100 patients as his or her primary care responsibility. Most fellows spend 6 months at the Clinical Center, NIH, and 6 months at the NNMC during the clinical year. The clinical research studies involve a wide variety of diseases and represent a collaboration between the intramural Clinical Oncology Program Branches and the NNMC.

The laboratory investigations of the branch revolve about human tumor cell biology and include studies of cell culture, somatic cell hybridization, cell kinetics, molecular biology, production of monoclonal antibodies by hybridomas, identification of tumor cell growth factors and pathways of differentiation, and human tumor cell genetics using gene transfer techniques. A major effort involves growing tumors from individual patients and selecting therapy after *in vitro* drug and radiation therapy sensitivity testing (human tumor clonogenic assay). The program is designed to include clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interest and goals.

Pediatric Oncology Branch—
Philip A. Pizzo, M.D.

The Pediatric Oncology Branch conducts clinical and laboratory research activities related to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, Ewing's sarcoma and neuroblastoma. Children and adolescents are accepted for treatment. Three areas of clinical investigations are stressed: chemotherapy with new or established agents; hematologic support and bone marrow transplantation; and diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 30 inpatient beds and an extensive outpatient department. The branch also has an extremely active teaching program, with 12 weekly clinical and laboratory conferences and seminars. Candidates with prior training in pediatrics may apply to this branch and are eligible for Board certification in pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical, surgical, and/or radiotherapeutic means, followed by experimental manipulation to prolong remission.

Comprehensive immunologic assays are performed to assess the natural history of these diseases and the influence of treatment.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. In conjunction with the Medicine Branch, a major area of interest is hematologic reconstitution through autologous bone marrow and stem cell transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised patient. These maneuvers include the use of laminar-air-flow isolation and prophylactic antimicrobial agents, as well as methods to bolster host defenses.

In the second and third year of this program, clinical research training is offered in the areas previously described. In addition to clinical research, the branch has a strong program in basic laboratory investigation with emphasis on tumor cell biology, molecular biology, clinical pharmacology, tumor immunology, hematopoiesis, and immunoregulation.

Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates by utilizing excellent collaborative relations with other branches of the NIH.

Radiation Oncology Branch—
Eli Glatstein, M.D.

The Radiation Oncology Branch of the National Cancer Institute offers a 3-year training program in radiation oncology. This program is organized in conjunction with the Uniformed Services University of the Health Sciences, through Walter Reed Army Medical Center and the National Naval Medical Center in Bethesda. The program calls for 18 months at the NCI, 9 months at Walter Reed, and 9 months at the NNMC.

The program emphasizes all aspects of patient care in radiation therapy with major emphasis on treatment planning and dosimetry. Experimental approaches are emphasized within the National Cancer Institute as part of prospective clinical trials; conventional treatment approaches are emphasized at the military facilities. Work on radiation sensitizing compounds, radioprotecting compounds, intraoperative irradiation, and atypical fractionation schemes will be ongoing at NCI. Areas of investigation include primary breast cancer, pancreatic carcinoma, carcinoma of the bladder, small cell carcinoma of the lung, lymphoma, Hodgkin's disease, gliomas, mycosis fungoides, soft tissue sarcomas, and pediatric neoplasms. Opportunities for study of a wider spectrum of conditions are available through the military hospitals, with special attention to head and neck cancer and gynecologic neoplasms. The emphasis at all institutions will be on combined modality approaches and on long-term follow-up to assess success and morbidity.

Preference will be shown to candidates who have completed all or part of training in another oncologic specialty. The director of training for the program is Eli Glatstein, M.D., Radiation Oncology

Branch, National Cancer Institute. Interested individuals should contact him.

Surgery Branch—
Steven A. Rosenberg, M.D., Ph.D.

This branch, a surgical oncology unit, emphasizes a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen, including sarcomas, rectal, breast, esophageal, and pancreatic cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy, as well as the development of new surgical techniques. Laboratory efforts are closely related to clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, X-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch physicians also serve as general surgeons to the entire NIH and see a variety of general surgical consultations not related to the field of cancer.

Developmental Therapeutics Program—
John Driscoll, Ph.D., Acting Associate Director

This program is a broadly based endeavor which promotes and supports all pertinent activities essential to preclinical development of new treatment modalities for cancer, particularly chemotherapy. A systematic search is conducted for potential antitumor agents. These are subjected to programmed preclinical evaluation according to a scheme called the Linear Array. In this approach the program is responsible for all preclinical phases of development including acquisition and synthesis of materials, isolation and production of diverse natural products, screening, pharmaceutical development, toxicology, and pharmacology.

The Office of the Associate Director is responsible for overall administration of a large intramural research program and an extramural program on preclinical development of therapeutic modalities.

Medical Staff Fellows

First-year medical staff fellows in the Clinical Oncology Program are eligible to work in the laboratories of the Developmental Therapeutics Program (DTP) for their second and third years of research training. The following paragraphs describe current projects from which medical staff fellows may elect to participate.

Laboratory of Chemical Pharmacology—
Richard L. Cysyk, Ph.D., Acting

This laboratory brings together scientists who play an important role in the use of pharmacologic information—plasma levels, tissue levels, mechanism of action, transport and metabolism studies—for experimental chemotherapy and earlier development and use of cancer chemotherapeutic agents for the clinic.

The pharmacologic properties of potential and established antitumor agents are evaluated *in vitro*, in animals and humans. These studies include evaluation of the antitumor activity of single agents, adjuvant and combination chemotherapy, and other modalities for cancer therapy. Other studies involve investigations on mechanism of action, structure-activity relationships, transport, dose-response relationships, effects on the immune system, mutagenic and carcinogenic potential of antitumor agents, and their disposition in laboratory animals and humans. The latter studies include the establishment of rates and rate constants that govern the passage of drugs from one body compartment to another.

Laboratory of Medicinal Chemistry and Biology—
David G. Johns, M.D., Ph.D.

This laboratory conducts an integrated program on the development of antitumor agents. Compounds with potential antitumor activity are synthesized, and effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites, e.g., nucleic acids, nuclear proteins, microtubular protein, and enzyme systems. Analytical methodology for *in vivo* studies with new agents is developed and, where warranted, biological studies with these agents are extended to the preclinical and Phase I stages. A contract-supported program to characterize the mode of action of new antitumor agents is also managed here. This laboratory stresses rapid and continuous utilization of the data generated from biological studies for elucidation of structure-activity correlations for guidance in synthesis of new antitumor agents of potential clinical value.

Laboratory of Molecular Pharmacology—
Kurt W. Kohn, M.D., Ph.D.

Mechanisms of action of anticancer agents are studied in culture and subcellular systems with particular attention to effects involving DNA and nuclear proteins. These investigations focus on the relation between drug-induced macromolecular damage (and its repair) and cell survival. Secondly, drugs are used as probes of the structure and function of DNA and chromatin. Experimental approaches include cell culture, DNA macromolecular damage measurements, and nuclear protein fractionation techniques.

Laboratory of Experimental Therapeutics and Metabolism—
Michael R. Boyd, M.D., Ph.D.

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is in analytical and clinical pharmacology; qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents are studied in experimental systems, as well as in man in a clinical setting. Problems are selected for their relevance to the development and/or evaluation of new chemotherapy protocols, and frequently are pursued collaboratively with other NCI laboratories. The other major area concerns the elucidation of fundamental chemico-biologic interactions underlying chemical-induced cytotoxicity and carcinogenicity to specific target organs and target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target issue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic "activation" and "deactivation" systems are of interest as well as investigation of the biochemical, physiologic, and morphologic consequences in the *in situ* generation of alkylating metabolites both in normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemical-induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimal toxicity to normal tissues.

Laboratory of Tumor Cell Biology—
Robert C. Gallo, M.D.

The objectives of the Laboratory of Tumor Cell Biology are to develop, implement, and analyze data obtained from studies of cell proliferation, cell differentiation, and biochemical growth characteristics of normal and malignant mammalian cells both *in vivo* and *in vitro.* Particular attention is given to hematopoietic cells, their normal behavior, and especially changes seen during leukemogenesis. Because of unusual access to human blood cells and because of the interest of this group, there is special focus on human leukemias and lymphomas. It is anticipated that an enhanced understanding of cell regulatory mechanisms will permit the optimal use of antitumor agents in the therapy of cancer and the development of new approaches.

The Laboratory of Tumor Cell Biology is concerned with several biological and biochemical problems: Studies on the cellular and molecular origin and pathogenesis of human leukemia; biochemical control mechanisms involved in cell differentiation and neoplastic transformation are examined; tumor viruses of animals are used both as tools (to define and isolate genes and gene products important for growth in man) and to understand mechanisms of naturally occurring animal leukemias; studies designed to determine if humans have similar viruses (retroviruses) are and have been intensively studied; and studies on the biochemical events preceding mitosis. An understanding of these events appears essential to the control of proliferation, and information derived from such studies may lead to more effective inhibitors of neoplastic cell growth. Events leading to mitosis are also of interest since many of the effective antitumor agents are useful only when cells are in DNA replication or in mitosis. Phytohemagglutinin-stimulated human lymphocytes and tissue-cultured cells are the principal tools in these studies; Attempts to develop new approaches to cancer chemotherapy using information gained from basic cellular studies; Studies on the development of biochemical and immunologic markers for malignant cells are carried out. Biochemical and immunologic studies are also conducted in individuals with disorders associated with an increased incidence of neoplasia; Controls regulating cell growth and differentiation, and the process of malignant transformation in hematopoietic cells and; Growth factors (and their receptors) that control the growth and differentiation of blood cells have been isolated and are under intensive study, e.g., T-cell growth factor (TCGF), CSF, and related hematopoietic growth affecting molecules.

National Eye Institute

Carl Kupfer, M.D.,
Director
Carl Kupfer, M.D.,
Acting Clinical Director
Jin Kinoshita, Ph.D.
Scientific Director

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three medical staff fellows from those candidates who have completed an accredited 3-year ophthalmology program. Fellows spend time in both clinical and laboratory research including patient care activities.

In selection of medical staff fellows, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

The National Eye Institute has developed its clinical and research program into four major branches, the Laboratory of Vision Research, the Laboratory of Sensorimotor Research, the Office of Biometry and Epidemiology, and the Clinical Branch.

Office of Biometry and Epidemiology— Fred Ederer, M.A.

The Office of Biometry and Epidemiology conducts studies that tend to fall into the broad areas of clinical trials, natural history, and epidemiology.

The clinical trials section is now responsible for three national multiclinic trials involving vitrectomy, drugs, and photocoagulation, as treatments to prevent progression in patients with diabetic retinopathy. These studies include thousands of patients, and combine the skills of several disciplines, including clinical, statistical, and computer sciences. Data generated in these studies not only provide a base for treatment strategies, but permit investigation of the extent to which risk factors other than treatment are related to disease progression.

The epidemiology section generates data on the prevalence, incidence, and distribution of diseases of the eye. Such data are used to evaluate hypotheses on the causes of such diseases. Data sets from the Framingham Eye Study and the Health and Nutrition Examination Survey are being actively analyzed to explicate the risk factors for changes in the lens and retina. A major national study of the prevalence of visual acuity impairment and its causes will soon be under way.

Laboratory of Vision Research—
Gerald Chader, Ph.D.

The laboratory is engaged in research involving the following disciplines:

Biochemistry—This section conducts studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolism of photoreceptors are also under investigation. In addition, synthesis of sugar-containing polymers in the retina are being studied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

Experimental Embryology—This section identifies and characterizes the myriad tissue interactions that control orderly growth of the vertebrate eye and assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ. Because most congenital defects of the eye are attributable to interference with these interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. Researchers are determining which tissues are responsive to such influences, the duration of these potencies and competencies during embryogenesis, the specificities of these interactions, and the nature of interactions which control morphogenesis.

Particular attention is being focused on newly discovered, cellfree, collagen-containing ''initiator layers'' which are transiently produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of the body.

Experimental Pathology—Research being conducted in this section centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of intraocular pressure on eye tissue, the damaging effect of light on the retina, laser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

Neurophysiology—Investigations on the cellular organization underlying visual perception are currently under way in this section. Studies are being conducted on the responses of single nerve cells at various levels in the visual nervous system of mammals. The purpose of this work is to understand how nerve cells contribute to visual sensations such as color, shape, movement, and depth. The technique employs fine microelectrodes which can be inserted into the brain in order to record from single nerve cells. It uses refined optical methods to enable an experimenter to stimulate the retina with spots or slits of colored lights whose movement and shape can be quantitatively controlled. It involves electrophorescing dye into single cells whose responses have been studied and then finding these cells within the brain or retina.

By this means both structure and function of nerve cells can be correlated and the underlying circuitry of the visual system understood. This approach requires close interaction between single cell physiology and cellular anatomy at the light and electron-microscopic level.

Retinal and Corneal Metabolism—This section is investigating the function of the retina, pigment epithelium, and cornea in relation to clinical diseases such as retinitis pigmentosa and keratomalacia.

The mechanism by which visual cells detect light and produce neural messages is not known. Calcium may play a role in the process since it mimics the effects of light on the retina and is found in very high concentrations in pigment epithelium and retinal photoreceptors. Small intracellular messengers called cyclic nucleotides have also been found in extraordinarily high concentrations in retinal photoreceptors. Since light markedly affects their concentration, they, too, are probably intimately involved in the visual process. A method of injecting various substances into visual cells is now being developed to determine directly the effect of these substances on the visual process in both normal and pathologic conditions.

Studies on the synthesis and degradation of the visual protein rhodopsin have helped explain how retinal photoreceptors are renewed. Defects in this process may underlie some forms of retinal degeneration; thus, studies using dystrophic retinas of test animals are under way to compare the process of photoreceptor renewal in normal and pathologic conditions. Substances such as hormones and neurotransmitters that affect the normal growth and development of retinal cells in tissue culture are being assessed. Several have already been identified and are being further studied in relation to their role in retinal function.

Specific receptor molecules for vitamin A have been found inr etina and pigment epithelium. These receptors are probably involved in the normal uptake, distribution, and retention of the vitamin in the visual system. Differences in receptor concentrations in retinas of normal humans and patients with retinitis pigmentosa have been found.

Vitamin A receptors are also present in the cornea and conjunctiva. The possible relationship of these receptors to corneal disease is being considered. Other aspects of corneal physiology, such as glutathione metabolism, are under investigation. Such studies are important not only for understanding corneal function and transparency but for improving corneal transplant and surgery techniques as well.

Laboratory of Sensorimotor Research— Robert Wurtz, Ph.D.

This laboratory conducts research on the central neural bases of vision and eye movements in the primate, and the application of these results to clinical problems in patients with visuomotor deficits. The laboratory uses a multidisciplinary approach, availing itself of techniques of neurophysiology, neuroanatomy, experimental psychology, psychophysics, systems engineering, and computer science.

One series of projects is designed to elucidate the central neural mechanisms in the control of visually guided eye movements. The activity of single neurons in cortical and subcortical areas is recorded using microelectrodes placed in the brains of behaving animals, in order to analyze the relationship of neural events to eye movements and the presentation of visual stimuli. Quantitative studies of eye movements are performed in animals with lesions in those brain areas which physiological recordings have indicated may be important in the neural mechanisms underlying eye movement and visual perception. The anatomic connections of these areas of interest are studied using axoplasmic transport methods.

A second series of experiments investigates the visual processing underlying visual perception. These experiments correlate the discharge of single cells within cortical and subcortical regions of the brain with the stimulus presented to the monkey.

In another series of studies the vestibulo-ocular system is used as a tool to study the mechanism by which the brain can adjust to environmental changes. This adaptive plasticity is studied using systems analysis of single neuron discharge patterns recorded from performing animals, and analysis of the performance of monkeys, normal human subjects, and patients with oculomotor deficits.

The ability of patients with visuomotor deficits is studied using paradigms for performance that have been developed using normal humans and monkeys, in order to study residual abilities following damage to discrete brain areas, and to develop strategies for rehabilitation of brain-damaged patients.

Since recent advances in sensorimotor physiology and psychophysics have been made possible by developments in the application of the online laboratory computer to these problems, a significant effort in the laboratory is the development and refinement of computer methods for the control and analysis of experimental results.

Laboratory of Molecular and Developmental Biology—
Joram Piatigorsky, Ph.D.

This laboratory conducts basic research on cellular and molecular biology. Emphasis is given to molecular and developmental genetics. The research is designed to elucidate both normal and disease processes. Particular attention is given to hereditary diseases which can be studied at the gene level. Much (but not all) of the work uses eye tissue as models for general problems concerning cellular differentiation and gene expression. Normal and pathogenic visual processes are also being related to the structure and function of genes.

Three major gene families are currently being investigated; namely, crystallins, opsins, and collagens. DNA clones are being constructed, analyzed, and used as probes for understanding a variety of normal and pathogenic circumstances. Phospholipid metabolism—particularly at the cell membrane—is also under investigation in order to advance our knowledge of cellular differentiation and differential gene expression.

Clinical Branch—
Carl Kupfer, M.D.

The branch plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of visual system disorders. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the branch's responsibility to investigate the causes and prevention of visual impairment.

- Cataract Section—
  Jin Kinoshita, Ph.D.

Cataracts of unusual origin and congenital cataracts are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

- Section on Neuro-opthalmology—
  David B. Cogan, M.D.

Patients from the ophthalmic and neurologic services are being studied using advanced methods for electrooculography, pupilometry, videotape recording, and computer analysis. The main emphasis of these studies is on cerebellar disorders that affect ocular movements.

- Section on Glaucoma—
  Douglas E. Gaasterland, M.D.

Intraocular fluid dynamics in normal and glaucomatous eyes and their alteration by pharmacologic agents are being studied. A controlled clinical trial to test the value of early treatment of ocular hypertension is under way. Innovative surgical techniques are being assessed in selected cases of primary, secondary, and congenital glaucoma in cases which antiglaucoma surgery has failed. The properties of trabecular meshwork are being studied in tissue culture.

- Section on Ophthalmic Genetic Studies—
  Muriel I. Kaiser, M.D.

These include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogenesis of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

The pathogenesis of unusual types of congenital or developmental anomalies of the eye is being studied under protocol. These cases include pigment dispersion syndrome, progressive essential iris atrophy, oculocutaneous albinism, and abnormalities of the anterior chamber angle associated with glaucoma.

- Section on Retinal and Ocular Connective Tissue Diseases—
  Muriel I. Kaiser, M.D.
  Monique Roy, M.D.

Retinal deteriorations—Clinical, biochemical, cell biological, and metabolic investigations are being conducted to define underlying mechanisms in diseases such as senile macular and related degenerations and the maculopathy of retinitis pigmentosa. Macular edema is also of special interest. The retinal pigment epithelium, its normal function, pathophysiology, and interrelationships are of special interest. Family studies of macular and retinal degenerations are emphasized.

Vascular diseases—Clinical investigations are being conducted in the treatment and underlying mechanisms of diabetic retinopathy.

Ocular connective tissues—Characterization and purification of extracellular matrix molecules synthesized by normal and abnormal ocular tissues, immunofluorescent antibody studies, and the enzymology and immunology of corneal melting are being investigated actively.

- Section on Ophthalmic Pathology—
  Merlyn Rodrigues, M.D., Ph.D.

Surgically excised biopsy material and eyes obtained from autopsies or enucleations performed at the Clinical Center are processed and studied by light and electron microscopy. Many of these specimens are from subjects with unusual metabolic and genetic diseases, glaucoma, and retinal disorders. Some of these specimens are further investigated by immunohistochemical techniques. The ocular effects of diabetes in animals, S-antigen uveitis, and chemotaxis induced by synthetic mediators have been studied in collaboration with investigators from other institutes at NIH. There is also opportunity for research on corneal diseases and glaucoma and for further investigation of mediators of ocular inflammation and animal models of diabetes.

A 2-year training program in clinical and experimental eye pathology is available under the supervision of Drs. Cogan, Kuwabara, and Rodrigues. This program includes experience in histochemistry and electron microscopy.

- Section on Ocular Immunology—
  Robert B. Nussenblatt, M.D.

Immunologic mechanisms relating to ocular inflammatory disease are being studied. The possible role of ocular autoimmunity in uveitis is being actively investigated. Patients with posterior uveitis, i.e., toxoplasmosis, pars planitis, birdshot choroidopathy, and sarcoid are being sought in order to evaluate their immunologic responses. The evaluation of patients with ocular inflammatory disease also includes monitoring their ocular physiologic responses during disease and when the inflammation is quiescent. The relationship of HLA and the immunologic response of patients with ocular inflammatory disease to antigens is being looked at, as are other immunologic factors, such as antibody production, suppressor cell activity, and macrophage responsiveness. Patients are in addition being sought for a controlled double masked study in the therapy of ocular toxoplasmosis.

National Heart, Lung, and Blood Institute

Claude Lenfant, M.D.
Director
Jack Orloff, M.D.,
Director of Intramural Research
Harry R. Keiser, M.D.,
Clinical Director

Candidates for research and clinical positions as medical staff fellows have only one interview in this Institute. Medical staff fellows are interviewed by a committee made up of the director of intramural research, the clinical director, and the deputy clinical director. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the National Heart, Lung, and Blood Institute (NHLBI). After appointment and prior to entering on duty each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the fellow and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. On the basis of past experience, it appears virtually certain that each fellow will be able to work with the group of his or her choice. The level of research responsibility and freedom will depend upon the fellow's training and experience as well as desires.

Each medical staff fellow will devote time primarily to research in the laboratory under the supervision of a preceptor in the area of selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of the laboratory.

All appointments as medical staff fellow are for a minimum of 2 years with a third optional year. In the past, most fellows have elected to remain for 3 full years and have been accorded this privilege.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research. Candidates must have satisfactorily completed a minimum of 2 years of residency training in general internal medicine in a program approved by the American Board of Internal Medicine by the starting date of their appointment. The first year of the clinical fellowship will be credited as a third year of training in internal medicine by the American Board of Internal Medicine if the candidate's clinical competence was satisfactory during the previous 2 years of training and is satisfactory here.

Medical staff fellows will be responsible, under the guidance of investigators on the NHLBI staff, for the primary medical care of research patients during 10 to 12 months of the first year of their service. During this time they will rotate through the four medical services that serve the clinically oriented branches of the Institute and assist in the work of the service with consultations and in the outpatient department. These services occupy 75 beds and include cardiology, hypertension-endocrinology, lung, hematology, and metabolism.

The clinical period is one of intensive training under direction of the clinical director and staff. It offers exposure to case material of extraordinary range and to highly sophisticated approaches to investigation of disease.

The fellow devotes both time off the wards and a full 12-14 months of the 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either* *clinical or nonclinical.* No clinical responsibilities are required during the second or the optional third year for fellows who have chosen nonclinical laboratories.

Medical Staff Fellows in Surgery

The Surgery Branch appoints five fellows yearly for a 2-year interval. These appointments are designed to give academically oriented surgeons-in-training an opportunity to initiate, participate and collaborate in both clinical and laboratory research. Candidates must have satisfactorily completed 2 core years of surgical residency training in a program approved by the American Board of Surgery. Cardiac physiology, biochemistry, pathology, prosthesis development, and perfusion instrumentation are emphasized. The clinical period of 9-12 months offers a large exposure to complex forms of heart disease and innovative methods for correction or palliation. The laboratory component involves multiple projects ranging from cellular biochemistry to large animal surgery. Interested candidates are encouraged to write to Richard E. Clark, M.D., Chief, Surgery Branch, NHLBI, Bldg 10, Room 2N242, National Institutes of Health, Bethesda, Maryland 20205.

Appointments in Laboratory Research

These appointments are designed to give highly qualified physicians an opportunity to do either clinical or basic research in any area of the Institute under the direct supervision of an experienced preceptor. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises.

Staff Appointments

Laboratories with the NHLBI sometimes have openings for medical staff fellows appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Checklist for the Institute. Selections for those positions are made by the chief of the branch or laboratory.

Joint Endocrinology Training Program

Medical staff fellows from the NHLBI may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to quality fellows for the Endocrinology Subspecialty Boards. NHLBI participants will spend an additional 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the fellow will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the fellow's 3 years will be spent primarily in research activity within the NHLBI, although he or she will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two NHLBI fellows to enter this program in any one year.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Medical staff fellows are expected to take advantage of this academic work. (See part 4, page 133.)

Clinical Research Branches

Cardiology Branch—
Stephen E. Epstein, M.D.

- Section on Cardiovascular Diagnosis—
  Douglas Rosing, M.D.

Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by various cardioactive agents, with particular emphasis on calcium antagonists. Major emphasis has recently been applied to the diagnosis and treatment of small coronary vasoconstriction, as well as the diagnosis and treatment of dynamic mechanisms precipitating myocardial ischemia.

- Section on Experimental Physiology and Pharmacology—
  Randolf E. Patterson, M.D.

Research is aimed toward understanding the physiologic, anatomic, and biochemical mechanisms responsible for control of the normal heart and coronary circulation, elucidation of the mechanisms causing ischemic and nonischemic heart disease, and evaluation of interventions designed to reverse the resulting abberations of cardiac function. Major interests are the study of the relation between atherosclerosis and coronary vasospasm, as well as elucidation of the role of vasoactive peptides in causing coronary vasospasm.

Clinical Hematology Branch—
Arthur W. Nienhuis, M.D.

The research activities in this branch, while diverse, are generally focused on the problems of red cell production, hemoglobin synthesis, and hemoglobin function. Syndromes of bone marrow failure, chiefly aplastic anemia, are investigated in the laboratory and with experimental therapeutic protocols. Stem cell function, cell-cell interactions, lymphocyte populations and their function, and the production of various hematopoietic factors are assayed by *in vitro* techniques to define the pathogenesis of bone marrow hypofunction. Experimental treatments under study include immunosuppressive and antiviral agents. Regulation of the several globin genes is being studied in the context of developmental switches in the hemoglobin phenotype in man and other species. Furthermore, the study of gene expression in patients with thalassemia is directed toward definition of molecular defects that result in deficient hemoglobin synthesis in these syndromes. Various strategies are being devised and tested with the long term goal of introducing functional genes into the erythroid cells of such patients. Treatment protocols include the evaluation of various cytotoxic drugs for their potential to stimulate fetal hemoglobin production in patients with thalassemia and sickle cell anemia.

Hypertension-Endocrine Branch—
Harry R. Keiser, M.D.

This branch represents a merger of the former Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension; activities are wide-ranging, as indicated by the description of section activities.

- Section on Experimental Therapeutics—
  Harry R. Keiser, M.D.

A wide spectrum of research opportunities is offered, ranging from basic biochemistry, physiology and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of the kallikrein-kinin system, renin-angiotensin-aldosterone system, prostaglandins and catecholamines and their interactions, conducted both in man and in experimental animals. Other studies encompass disorders of serotonin, histamine, and peptides.

- Section on Biochemical Pharmacology—
  Walter M. Lovenberg, Ph.D.

This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of enzymes responsible for the biosynthesis of neurohumoral amines. The role of these systems in disease states, particularly hypertension, is of prime interest, and investigations are extended from the molecular level to experimental animals and man.

Molecular Disease Branch—
H. Bryan Brewer, M.D.

The research activities of this branch are directed toward the elucidation of the molecular mechanisms involved in lipid transport and metabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis. Studies take several approaches employing protein chemistry, immunology, tissue culture, molecular biology, and enzymology. Clinical research is focused on the effects of drugs and therapeutic diets on dyslipoproteinemia and on kinetic analysis of the metabolic defects in patients with these diseases. Activities are integrated in such a way that, if medical staff fellows wish, they may participate in collaborative research involving several different areas.

Pathology Branch—
William C. Roberts, M.D.

This branch is concerned with the study of morphologic aspects of cardiovascular and pulmonary diseases and their correlation with functional derangements. Morphologic analyses include transmission and scanning electron microscopy.

Pulmonary Branch—
Ronald G. Crystal, M.D.

Research in this branch is designed to investigate the structure and function of the lung in health and disease through cellular and biochemical methods. Both laboratory and clinical investigations are conducted. Techniques of protein chemistry, molecular biology, tissue culture, and immunology are used. Emphasis is placed on the regulation of synthesis and degradation of connective tissue and on the inflammatory and immune processes in the normal and diseased lung. Clinical research is directed toward correlating physiologic, biochemical, immunologic, and morphologic observations in patients with interstitial lung disease, destructive lung disease, hereditary disorders of connective tissue, hypersensitivity lung disease, and other lung disorders with an immunologic basis.

Surgery Branch—
Richard E. Clark, M.D.

The clinical research programs are designed to span prospective longitudinal studies of surgical therapies to developing unique prosthesis and support systems for the critically ill cardiac patient. Major areas of interest include, but are not limited to, development of improved myocardial preservation techniques and definition of relevant end points, studies in bioprosthetic and new mechanical valvular prostheses, metabolic studies of pulsatile perfusion and membrane oxygenation, intrinsic coronary vasomotor tone alterations as a function of cardiac surgery. Other studies involve capillary permeability in pulmonary hypertension, development of small diameter vasular prostheses and new immunologic approaches to heart transplantation. Approaches to these areas are multidisciplinary and encourage interaction with biochemistry, biophysics, materials science, pharmacology, ultrastructural pathology, platelet pathophysiology and immunology. Didactic educational sessions include advanced clinical cardiac pharmacology, research conferences, statistical methods, Fellows clinical interdepartmental conference and a guest lecturer program.

Basic Research Laboratories

Laboratory of Biochemical Genetics—
Marshall Nirenberg, Ph.D.

- Section on Molecular Biology—
  Marshall Nirenberg, Ph.D.

Basic problems in molecular biology and biochemistry are studied in this section, particularly those that pertain to the development of the nervous system. Current research is focused on elucidating mechanisms that regulate gene expression using recombinant DNA techniques. Many monoclonal antibodies have been generated and are being used as probes for synaptic and other antigens. Cultured cells are used in many studies. Research also is being conducted on cyclic nucleotides, ion channels and cell recognition.

- Section on Macromolecules—
  Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms. One area of interest involves the hypothalamic tripeptide thyrotropin-releasing factor. The biological properties of some new derivatives of thyrotropin-releasing factor are under investigation. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells.

Laboratory of Biochemistry—
Earl R. Stadtman, Ph.D.

- Section on Enzymes—
  Earl R. Stadtman, Ph.D.

Studies of this group are concerned with the elucidation of various mechanisms of metabolic regulation, specifically, studies on the regulation of enzyme activities by allosteric interactions, by enzyme catalyzed covalent modification (phosphorylation, nucleotidylation, etc.) of interconvertible enzymes, and on the regulation of enzyme levels by changes in the rates of protein degradation medicated by mixed-function oxidase catalyzed inactivation of enzymes. These studies involve the isolation and characterization of key regulatory enzymes and of the enzymes which catalyze their covalent modification, oxidative inactivation, and proteolytic degradation.

- Section on Intermediary Metabolism and Bioenergetics—
  Thressa C. Stadtman, Ph.D.

This section is concerned primarily with investigations on the mechanisms of anaerobic metabolism of one-carbon compounds and amino acids and phosphorylation reactions coupled to the electron transfer processes. Emphasis is on the roles of various coenzymes (*e.g.,* vitamin B_{12} coenzyme, CoA, deazaflavins, quinones) and electron transfer proteins such as selenoproteins, molybdo-iron sulfur proteins and flavoproteins. The occurrence and roles of selenium in enzymes and amino acid transfer nucleic acids are being investigated currently.

- Section on Protein Chemistry—
  Ann Ginsburg, Ph.D.

Studies on protein structure in this laboratory are directed toward understanding the roles of ligand binding and of protein-protein interactions in enzyme catalysis and regulation.

- Section on Metabolic Regulation—
  P. Boon Chock, Ph.D.

This section conducts biophysical studies on various enzymes and proteins with emphasis on the mechanisms of enzyme action and its regulation. Currently, we are investigating the roles of covalent modification in metabolic regulation of enzymes. This involves the study of the glutamine synthetase cascade and the phosphorylation/dephosphorylation cascade. In addition, we are studying the mechanism for the activation of cyclic nucleotide phosphodiesterase and calcineurin by calmodulin, enzyme-monoclonal antibody interaction, and glutamine synthetase catalysis.

Laboratory of Cell Biology—
Edward D. Korn, Ph.D.

This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

- Section on Cellular Biochemistry and Ultrastructure—
  Edward D. Korn, Ph.D.

This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the molecular and ultrastructural basis of cell motility. Cytoplasmic actin, myosin, and related proteins are purified from nonmuscle cells and their interactions studied and compared to their muscle counterparts. Currently, emphasis is on the regulation of actin polymerization, the regulation of actin-activation of myosin-ATPase, and the characterization of multiple myosins in a single cell. Opportunities are available for research and training in biochemistry and electron-microscopy.

- Section on Cellular Physiology—
  Evan Eisenberg, M.D., Ph.D.

This section conducts studies on the molecular events of muscle contraction including the interaction of actin and myosin with each other and with the control proteins, tropomyosin, and the troponins. Emphasis is on kinetic studies with pure proteins.

- Section on Membrane Enzymology—
  Richard Hendler, Ph.D.

This section studies enzyme systems that require organization on, or interaction with, membranes in order to ensure their proper functioning. The electron transport chains of *Escherichia coli* and mammalian mitochondria are presently being investigated.

- Section on Organelle Biochemistry—
  Martin Flavin, M.D., Ph.D.

This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the physiologic regulation of assembly and function. At this time the major emphasis is on the mechanism of polymerization of microtubules in brain and unicellular organisms.

Laboratory of Cellular Metabolism—
Martha Vaughan, M.D.

- Section on Metabolic Regulation—
  Martha Vaughan, M.D.
- Section on Biochemical Physiology—
  Vincent C. Manganiello, M.D., Ph.D.
- Section on Molecular Mechanisms—
  Joel Moss, M.D., Ph.D.

Research is directed at understanding the regulation of cyclic nucleotide synthesis and degradation. cAMP synthesis by the membrane-associated adenylate cyclase complex is controlled by stimulatory and inhibitory agonists (hormones, drugs), acting through cell surface receptors. The signal generated by receptor-agonist interaction is transmitted to the cyclase catalytic unit via GTP-dependent coupling proteins, which are also the targets for covalent modification (ADP-ribosylation) catalyzed by bacterial toxins (*e.g.,* cholera toxin, pertussis toxin) that activate the cyclase. Areas of current study include:

Cell Biology: effects of hormones and toxins on cyclic nucleotide content and formation of arachidonate metabolites (*i.e.,* prostaglandins, leukotrienes) by cultured cells; Membrane Biochemistry: molecular mechanisms for interaction of adenylate cyclase components, analyzed, in part, with site specific monoclonal antibodies; kinetics of receptor-ligand interaction; effects of toxin-catalyzed ADP-ribosylation on the interaction of coupling proteins with receptors and catalytic unit; Enzymology: identification of ADP-ribosyltransferases and their substrates in animal cells; effects of ADP-ribosylation on enzyme function; regulatory properties of phosphodiesterases that degrade cyclic nucleotides; mechanisms by which calmodulin modifies activities of phosphodiesterase and other proteins with which it interacts; and Molecular Biology: regulation of gene expression for components of the adenylate cyclase system; effects of translational control on production of cyclase components.

Laboratory of Chemical Pharmacology—
James R. Gillette, Ph.D., Chief
Michael A. Beaven, Ph.D.
Deputy Chief

- Section on Drug-Enzyme Interaction—
  James R. Gillette, Ph.D.

The interests of this section center on various aspects of drug disposition including pharmacokinetics and the relationship between drug metabolism and drug toxicity. Its main objectives have been understanding the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

- Section on Drug-Tissue Interaction—Gopal Krishna, Ph.D.

This group is involved in the study of the initial events occurring in cells as the result of a variety of drug-hormone cell interactions, including the role of cyclic nucleotides as mediators of a variety of hormone actions. Recently, this section has become involved in the investigation of the biochemical mechanisms that may be involved in drug-induced tissue lesions.

- Section on Cellular Pharmacology Michael A. Beaven, Ph.D.

This section studies mechanisms of release and action of inflammatory mediators, especially in isolated cell systems. Current work includes studies of the role of Ca^{++} in the mechanism of mast cell degranulation in freshly isolated and cultured mast cells and basophils, the properties and cellular location of enzymes involved in histamine synthesis and degradation, the role of vascular endothelial cells in the generation and destruction of inflammatory mediators, and the effect of drugs on mediator release in animal models of inflammation and identification of factors responsible for changes in vascular permeability and white cell recruitment.

- Section on Pharmacological Chemistry—Lance R. Pohl, Ph.D.

This section studies the mechanisms of metabolism, action, and toxicity of pharmacologically active chemicals. It includes studies of the identication of active substances formed in the body, the characterization and regulation of the enzymes that either produce or metabolize these agents, and the biochemical basis of their pharmacologic and toxicologic actions.

Laboratory of Chemistry—
Henry M. Fales, Ph.D.

This laboratory conducts research on methods for the structural analysis of organic compounds and investigates their biological function. Specialties are mass spectrometry, nuclear magnetic resonance, X-ray crystallography, advanced chromatography, advanced chromatographic methods, radioimmunoassay, and data retrieval techniques. Collaborative studies are carried out with other chemists, clinicians, and biologists.

- Section on Physiological Chemistry—John J. Pisano, Ph.D.

The Section on Physiological Chemistry studies normal and pathological states in man at the molecular level. Under investigation are biologically active peptides (vasoactive and neuroactive), precursor proteins of the peptides, and the enzymes involved in their biosynthesis and degradation. Modern analytical techniques such as gas chromatography, high-performance liquid chromatography, affinity chromatography, mass spectrometry, and radioimmunoassay are commonly employed. Research is currently directed to the study of hypertension, new factors regulating coagulation and fibrinolysis, micro methods for the detection and the amino acid sequence analysis of polypeptides, and the discovery of naturally occurring biologically active peptides using a variety of bioassay techniques.

- Section on Chemical Structure—Henry M. Fales, Ph.D.

This group isolates and identifies biochemically important and structurally interesting organic compounds using gas, liquid, high-pressure, and thin-layer chromatography in conjunction with mass spectrometry, nuclear magnetic resonance, and X-ray crystallography. The section also develops and extends methodology in above fields. Typical applications include drug metabolites, acidic components of urine in diseased states, analysis of cardiovascular drugs insect and plant toxins, and synthetic intermediates.

- Section on Structural Nuclear Magnetic Resonance—Robert H. Highet, Ph.D.

The section emphasizes the development and use of new techniques to study the structure and chemical characteristics of compounds of biological interest. The structure of metabolites of steroidal drugs and alkaloidal toxins and the factors influencing aromatic-alicyclic tautomerism are typical areas for investigation.

Laboratory of Kidney and Electrolyte Metabolism—
Maurice B. Burg, M.D.

- Section on Electrolyte Transport—Jack Orloff, M.D.
- Section on Renal Mechanisms—Maurice B. Burg, M.D.
- Section on Membrane Metabolism—Joseph S. Handler, M.D.

This laboratory conducts research on the mechanism and regulation, hormonal and otherwise, of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, and epithelial cell cultures. Electrophysiology and intermediary metabolism as related to transport are emphasized.

Laboratory on Molecular Cardiology—
Robert S. Adelstein, M.D.

Current investigations are directed toward understanding the function and regulation of contractile proteins in muscle and nonmuscle cells. The role of cyclic nucleotides, calcium, calmodulin, and myosin phosphorylation in regulating actin-myosin interaction is of particular interest. Projects include myosin phosphorylation and the regulation of kinases and phosphatases in smooth muscle, heart, and nonmuscle cells such as brain, blood platelets, and myoblasts. The role these proteins play in cellular development, differentiation, and tumorigenicity is of current interest.

Laboratory of Molecular Hematology—
W. French Anderson, M.D.

This laboratory is concerned with investigation into the mechanism and regulation of mammalian gene expression, specifically in relation to hemoglobin biosynthesis. Areas of research include molecular cloning of globin and gene transfer of globin (and other) genes by physical microinjection and cellular transformation techniques into mice, other genes, cell-free transcription of cloned genes, studies on globin gene expression using mouse erythroleukemia cells, somatic cell hybrids, and mouse models of the thalassemias. Joint studies are also carried out with the Clinical Hematology Branch.

Laboratory of Technical Development
Robert L. Bowman, M.D.

This laboratory conducts research on instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicromethods to practical clinical instrumentation.

- Section on Biophysical Instrumentation—Robert L. Berger, Ph.D.

This section develops methods and instruments based on new physical and computer science technology to measure reaction kinetics, molecular structure, and chemistry of substances of biomedical interest. Current work involves developing calorimetric, Mossbauer spectroscopic, laser photolysis, fast spectroscopic, and fluorometric systems.

- Section on Pulmonary and Cardiac Assist Devices—
  Theodor Kolobow, M.D.

This section conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This includes the development of improved blood oxygenators, blood pumps, and control systems.

National Institute on Aging

T. Franklin Williams, M.D.,
Director
Richard C. Greulich, Ph.D.,
Scientific Director
Reubin Andres, M.D.,
Clinical Director

Medical Staff Fellows

The Intramural Research Program of the National Institute on Aging (NIA) is located at the Gerontology Research Center (GRC) in Baltimore, Maryland and at the NIH in Bethesda. The clinical and basic programs of the laboratory of Neurosciences are located at the NIH Clinical Center, Bethesda, Maryland.

The multidisciplinary program of the GRC, located on the campus of Baltimore City Hospitals, offers 2-year clinical and basic research training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, medical staff fellows may participate in clinical activities of Baltimore City Hospitals and the nearby Johns Hopkins Hospital. Two-year fellowship appointments may be extended in special instances to 3 years. On occasion, such extended programs, which include clinical experience, may serve to qualify the individual for certification by a medical subspecialty board.

In addition to the 2-year appointment limited to laboratory research at the center, there are two 3-year programs of combined clinical and research training in collaboration with the Johns Hopkins University and its major teaching affiliate, the Baltimore City Hospitals. These special programs are in cardiology, psychiatry and in geriatric medicine. They are offered to a limited number of candidates each year. In each program the first year is usually spent in clinical training as a resident physician or clinical fellow and the second and third years are spent in clinical or laboratory research at the Gerontology Research Center.

For example, the first year of the geriatric medicine program involves clinical training both at the Baltimore City Hospitals and in the Johns Hopkins Department of Medicine. It includes rotations through an inpatients consultation service, home care program, long-term institutional care at both skilled and chronic hospital levels, rehabilitation, and ambulatory care. The subsequent 2 research years are spent in one of the clinical or basic research laboratories described below in accord with the aptitudes, experience, and career goals of the individual fellows.

Medical staff fellows are encouraged to participate in seminars conducted by the NIA center's staff who present a comprehensive view of research in aging and related topics. Weekly research conferences are presented by staff members and invited lecturers.

A primary resource for clinical investigation on human subjects is the Baltimore Longitudinal Study of Aging. The subjects are volunteers, 20 to 96 years old or more, who reside in the community, who return for extensive studies every 2 years, spend 2½ days as inpatients each visit, and are enrolled for their entire lives. The study of men is now of 25 years' duration and involves 650 active participants; the study on women began in 1978 and its size will eventually be comparable to the male sample. The women's cohort currently numbers more than 350. Medical staff Baltimore-based fellows are required to participate in the routine physical examinations of these subjects.

In support of its research program, the center maintains extensive animal colonies to provide rats, dogs, and rabbits of known age, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment and photography and arts services. Computer facilities are also available, and instruction in the use of computers for laboratory research is provided. The library of the center contains one of this country's most extensive collections of literature on aging research as well as standard scientific journals.

The Laboratory of Neurosciences, located at NIH's Clinical Center in Bethesda, Maryland offers 2 years of both clinical and basic research training. In addition, there is the potential for a third or fourth year of study.

Prospective candidates wishing further information should write to either Richard C. Greulich, Ph.D., Scientific Director, or Reubin Andres, M.D., Clinical Director, NIA Gerontology Research Center, Baltimore City Hospitals, 4940 Eastern Avenue, Baltimore, MD 21224. Prospective candidates wishing specific information about the Laboratory of Neurosciences should write to: Neal A. Cutler, M.D., Deputy Clinical Director, NIA, Building 10, Room 10N314, Bethesda, MD 20205.

Clinical Research Branches

Clinical Physiology Branch—
Reubin Andres, M.D.

This branch is primarily concerned with studies on physiologic changes occuring over the entire adult lifespan. Studies include the quantification of age changes, elucidation of mechanisms underlying these changes, and relationships between aging processes and specific disease states.

- Endocrinology Section—
  Robert I. Gregerman, M.D.

This section conducts studies on the molecular basis of age-related changes of hormone responses, especially those related to the biochemistry of the adenylate cyclase system and hormone receptors; aging and the endocrinology of the reproductive system; and the enzymology and peptide chemistry of the renin-angiotensin system. Clinical studies are conducted on subjects from the Baltimore Longitudinal Study of Human Aging. Studies on rodents are done on a variety of organs; hormone studies are done in animals of all ages.

- Cardiovascular Section—
  Edward G. Lakatta, M.D.

Scientists in this section investigate cardiovascular hemodynamic function in man using noninvasive methods that include studies both in normal and cardiovascular disease states. Studies on isolated cardiac muscle focus on the mechanisms that govern excitation-contraction coupling. Additional studies investigate the effect of age, hypertrophy, and physical conditioning on electrophysiological, contractile, and biochemical parameters in cardiac muscle. Response to stress such as hypoxia and adrenergic stimulation and other pharmacological interventions are also studied in these animal models.

- Metabolism Section—
  Reubin Andres, M.D.

This section emphasizes research on glucose homeostasis and its endocrine control. Factors controlling insulin secretion, including gastrointestinal insulinotropic hormone, are quantified with the use of servo-control glucose clamp technique. Clinical investigations in man are concerned with the assessment of interrelations among such variables as age, obesity, diabetes mellitus and its complications, serum lipids, dietary factors, and physical activity. Biologic rates of aging in multiple systems are also assessed. The isolated perfused rat pancreas preparation supplements human studies.

- Clinical Immunology Section—
  William H. Adler, M.D.

Studies are conducted on the decline in host immune responsiveness that is seen in aging. These studies involve the development of diagnostic procedures for the detection of relative immunodeficiencies in humans and the investigations of the mechanisms of these deficiencies in humans and experimental animals.

- Human Performance Section—
  Jordan D. Tobin, M.D.

This section supports the Baltimore

Longitudinal Study of Human Aging with work in a variety of areas. Body composition studies seek the causes of tissue loss in the aged. Exercise physiology research is designed to determine the causes of reduced physical capacity in old age. Habitual physical activity and nutrition of subjects are monitored. Assessments are made of neuromuscular function, psychomotor capacity, hearing, and vision. Pulmonary physiology is studied in the context of genetic and environmental factors. Other work includes studies of the relationship of blood pressure to psychomotor variables and intelligence; dermatoglyphics in disease, world populations, twins, and aging; and the factors underlying reduced sexual function in the elderly.

Laboratory of Neurosciences—
Stanley I. Rapoport, M.D.

The laboratory's clinical program investigates cerebral metabolism in man in relation to aging and dementia. The laboratory also examines pharmacokinetics and peripheral metabolism of centrally acting drugs as a function of age.

- Brain Aging and Dementia Section—
  Neal R. Cutler, M.D.

This section operates a 6-bed Patient Care Unit at the Clinical Center as well as an outpatient Dementia Clinic. Physicians, psychologists, pharmacologists, and physiologists work together in research activities focused primarily on aging of the central nervous system, and on dementia and associated neurological diseases as these relate to the elderly. Aging of men and women, between the ages of 21 and 85, is examined in a longitudinal program with particular emphasis on cognitive function and activity. Patient groups include those with Alzheimer's dementia, multi-infarct dementia, and Down's syndrome, as well as with other relevant central nervous system diseases. Patients are recruited for inpatient protocols via the Dementia Clinic, which also addresses issues of epidemiology and incidence of disease processes. Methods employed include neuropsychometrics, biochemical analyses of neurotransmitters and their metabolites, physiological measurements of activity and neurological competence, and techniques to measure cerebral metabolism and brain structure. Positron emission tomography (PET scanning) is a critical tool of the program, for the examination of cerebral metabolism *in vivo*. The results are correlated with quantitative neuropsychometric evaluation of cognitive and sensorimotor functions.

Particular attention also is paid to the careful clinical evaluation of the noradrenergic and dopaminergic systems, through the use of biochemical and pharmacological explorations, in the areas of normal aging, essential hypertension, and related disorders.

The clinical pharmacology of aging is another area of interest for our clinical program and includes the careful evaluation of the pharmacokinetics and pharmacodynamics of various antihypertensive and central nervous system drugs in the elderly.

Research on aging and dementia is frequently conducted in collaboration with other involved clinical and basic groups in other institutes at the NIH, on specific areas of common interest. Furthermore, protocols often are designed in collaboration with members of the Basic Section on Cerebral Physiology and Metabolism of the Laboratory of Neurosciences.

Basic Research Laboratories

Office of the Scientific Director—
Richard C. Greulich, Ph.D.

- Comparative Nutrition Section—
  Charles H. Barrows, Sc.D.

Scientists investigate the relationship between aging and nutrition in animal populations. The specific areas studied include the effects of age on absorption, distribution, and utilization of known nutrients and the mechanisms responsible for an increased lifespan associated with dietary restriction. These investigations are done with physiologic, biochemical, and electronmicroscopic techniques. Other studies deal with comparative mammalian biochemistry including investigations of the stability of gene control mechanisms and the characterization of chromatin.

- Experimental Morphology Section—
  Richard C. Greulich, Ph.D.

This section brings the most modern techniques of microscopy (TEM, SEM) and the related techniques of high resolution autoradiography and electron and X-ray probe microanalysis to bear on problems of structural-functional relationships during aging. Current interests include cell-cell interactions, junctional complexes, and epidermal aging.

Laboratory of Behavioral Sciences—
Bernard T. Engel, Ph.D.

- Psychophysiology Section—
  Bernard T. Engel, Ph.D.

This laboratory is primarily concerned with the application of behavioral and psychological techniques and principles to the control or mediation of physiologic responses. There are both clinical research programs in the area of behavioral medicine and basic research programs using animal models to study neural control of cardiovascular function, as well as central neurotransmitter changes with age.

- Learning and Problem-Solving
  Section—David L. Arenberg, Ph.D.

This section investigates the effects of aging on motor behavior, perceptual skills, learning, memory, and problem-solving ability. Laboratory facilities exist to measure cognitive and perceptual function in man.

- Stress and Coping Section—
  Paul T. Costa, Jr., Ph.D.

Investigators in this section examine personality and its influence on life-course patterns including health behaviors, career, family and leisure adjustment, and coping with life stresses. Research emphasizes individual assessment of behavior and personality and their relationship to a wide variety of outcomes. Longitudinal and multivariate approaches are used to evaluate predictors of psychological well-being and overall quality of life.

Laboratory of Cellular and Molecular Biology—
Gunther L. Eichhorn, Ph.D.

This laboratory conducts research basic to the aging process at the cellular and molecular levels, with emphasis on genetic information transfer. Highly qualified fellows have the opportunity to become familiar with the latest techniques for the solution of biological problems at the cellular and molecular level: NMR, CD, etc.

- Inorganic Biochemistry Section—
  Gunther L. Eichhorn, Ph.D.

This section studies the effects of metal ions on nucleic acid structure and on genetic information transfer, including chromatin structure and RNA synthesis. It is primarily concerned with the mechanisms of introducing error into genetic information transfer. NMR techniques are used to study age changes in cells and animals.

- Molecular Physiology and Genetics
  Section—George S. Roth, Ph.D.

Studies are carried out on the regulation of physiological functions during aging, especially those most critical to life maintenance, as influenced by endocrine, neuro-endocrine, nutritional, environmental, and genetic factors. Particular emphasis is placed on elucidating the molecular and biochemical age changes which occur in the regulatory processes.

- Macromolecular Chemistry Section—
  Josef Pitha, Ph.D.

Scientists in this section study the interaction of cells with synthetic macromolecules. Investigators probe age changes on the cell surface with specially designed macromolecules and also synthesize potential polymeric drugs.

Laboratory of Molecular Aging—
Bertram Sactor, Ph.D.

In this laboratory, highly qualified medical staff fellows have the opportunity to develop expertise preparing them for careers in basic medical research. The thrust of the biochemical, biophysical, and physiologic programs are directed toward the biology of membranes and cells (isolated and cultured). The studies encompass calcium and phosphorus homeostasis, salt/water balance, acid/base status, and other ion and protein transport systems in the kidney, GI tract, bone, heart, and parotid gland, and examine the mechanisms by which these systems are perturbed by various pathophysiological states, including aging. The problems and questions relate to: the molecular organization of the membrane; mechanisms of vectorial transport; hormonal and vitamin D_3 metabolite regulation of transport; altered transports in animal models for specific diseases and disturbances; isolation of carriers and reconstruction of functional synthetic membranes; alterations in the molecular conformation and function of membrane proteins with age utilizing monoclonal antibody technology; the turnover of proteins and lipids in membranes; and the failure to maintain membrane structure and function with age which leads to physiologic dysfunction and cell death.

- Intermediary Metabolism Section—
  Bertram Sacktor, Ph.D.
- Biophysics Section—
  Bertram Sacktor, Ph.D.

Laboratory of Neurosciences—
Stanley I. Rapoport, M.D.

This laboratory investigates the function, structure, physiology, biochemistry, and pharmacology of central and peripheral nervous systems and of muscle, and the changes that take place during development and aging in animal models and in man.

- Cerebral Physiology and
  Metabolism Section—
  Stanley I. Rapoport, M.D.

This section conducts fundamental research on animal models of human aging and disease, as well as collaborative research with the Clinical Section on Brain Aging and Dementia of the Laboratory. Areas of concern include neuropharmacology, the blood-brain barrier (ultrastructure, transport, and permeability), peripheral nerve function and morphology, cerebral metabolism, and synaptic transmission. Methods employed in the laboratory include integrative physiological techniques with whole animal preparations, tissue culture and electrophysiology, biochemical and analytical techniques (including HPLC, gas chromatography, mass spectrometry), mathematical modeling in relation to pharmacokinetics, autoradiography of brain structures (with the 2-deoxy-D-glucose technique and techniques to evaluate brain lipid and protein metabolism and blood flow), radiotracer techniques, histology, electromicroscopy, and biophysical approaches to physiology. Broad areas of concern to the neurosciences, as they relate to aging and development, are addressed.

National Institute on Alcohol Abuse and Alcoholism

Alcohol, Drug Abuse, and Mental Health Administration

Robert Niven, M.D.
Director
Laura Rosenthal
Deputy Director of Intramural Research
Markku Linnoila, M.D., Ph.D.
Clinical Director

The National Institute on Alcohol Abuse and Alcoholism conducts an intramural program of basic and applied research on the multiple determinants and processes of alcoholism and other alcohol-derived health problems. The clinical facilities and research laboratories are located at the National Institutes of Health Clinical Center in Bethesda, Maryland. Medical staff fellow appointments are available to conduct clinical and/or basic research investigations. Depending upon the appointment, certain fellows will also have clinical responsibilities.

Appointments in Clinical Research

Medical staff fellowship positions are available in neurology, internal medicine, psychiatry, experimental therapeutics, and developmental neurology. Fellows are appointed for 2 years with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on the NIAAA ward and involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NIAAA research emphases.

Candidates requiring further information about the clinical positions for medical staff fellows should write to Markku Linnoila, M.D., Ph.D., Clinical Director, DICBR, National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3B19, National Institutes of Health, Bethesda, Maryland 20205.

Appointments in Laboratory Research

NIAAA medical staff fellow positions are available for laboratory research in the Laboratory of Clinical Studies, Laboratory of Metabolism, and the Laboratory of Preclinical Studies. Appointments are for a 2-year period, with the possibility of extension.

Fellows will engage in research on contemporary biomedical problems. During their tenure, fellows will devote the larger portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities.

Research experience is gained through the process of personal guidance by senior scientists who are preceptors. Areas of study are developed by each fellow in conjunction with the preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned.

Medical staff fellows have the opportunity to work closely with a diverse group of senior investigators, to participate in courses, conferences and seminars, and to employ advanced research methodologies in the course of their research.

For further information on the NIAAA Medical Staff Fellowship Program, write to the Deputy Director, Intramural Research Program, National Institute on Alcohol Abuse and Alcoholism, Building 10, Room 3C218, Bethesda, Maryland 20205.

Laboratory of Clinical Studies—
Markku Linnoila, M.D., Ph.D.

The major research interests of the laboratory concern effects of acute and chronic consumption of alcohol in humans. Furthermore, blood relatives of alcoholics at a high risk of developing alcoholism will be compared to age and sex matched subjects without a family history of excessive drinking or alcoholism. The general areas of inquiry are broadly defined by the names of the sections and units in the laboratory: Section of Clinical Science (Peter R. Martin, M.D.); Section of Clinical Brain Research (Michael Eckardt, Ph.D.); Section of Clinical Biochemistry and Pharmacology (Markku Linnoila, M.D., Ph.D.); Section of Analytical Biochemistry (Norman Salem, Ph.D.); Section of Neuroscience (Robert Eskay, Ph.D.); Unit of Genetic Studies (David Goldman, M.D.); and the Unit of Family Studies (Yolande Davenport, M.S.W.). The techniques available include EEG-telemetry, sleep recording, activity and temperature monitoring, evoked responses, brain imaging, neuropsychological testing, advanced computer analyses of blood chemistry profiles, drug concentration measurements with liquid chromatrography, monoamine and neuropeptide analyses with liquid chromatography, membrane lipid analyses with mass fragmentography, receptor studies, and animal behavioral pharmacology. The aims of the program are to test and develop new approaches for the treatment and prevention of alcoholism and its complications as well as to train professionals to work successfully in the field of alcohol research.

Laboratory of Metabolism—
Richard Veech, M.D., D.Sc.

The Laboratory of Metabolism conducts studies in basic biochemistry, clinical metabolic studies on patient samples, genetic studies with fibroblasts, and molecular biology, including studies with recombinant DNA and peptide synthesis. The aim is to provide the most appropriate tehcniques to solve the particular problem at hand.

The basic biomedical studies include the kinetics of alcohol dehydrogenase, PPi-PFK microsomal monooxygenases and the PRPP phosphoribosyl phosphotransferases. Thermodynamic studies are under way covering a number of areas including the purine salvage pathway and the carbonylphosphate synthase reaction. Metabolic studies defining the control points switching amino acids from ureagenesis to protein synthesis are under way as are studies involving glycogen synthesis, c-AMP and Co effects as well as certain metabolic inhibitors' effects on mitochondrial shuttles. Blood samples from alcoholic patients are examined to determine the nature and source of abnormal metabolites found and the contribution that genetic versus induced enzymatic changes play in inducing these abnormalities. The question is pursued further using cultured fibroblasts from alcoholic and non-alcoholic subjects as well as individuals with a variety of other known genetic diseases.

Finally, peptide fragments and analogues for various pituitary peptides are being synthesized from c-DNA fragments and by solid state peptide synthesizer and are being tested for biological activity.

Laboratory of Preclinical Studies—
Forrest F. Weight, M.D.

A broad program of investigation is conducted on physiological, pharmacological, and chemical properties of nervous tissue and the relationship of these properties to the functional activity of the nervous system. Current experimental studies involve two main areas: the physiology and pharmacology of neurons and synapses in the central and peripheral nervous system; and the molecular mechanisms involved in regulating neuronal excitability and membrane permeability in nervous tissue.

Studies on the physiology and pharmacology of neurons and synapses involve primarily electrophysiological techniques such as current-, voltage-, and patch--clamp methods to study the regulation of neuronal excitability and the ionic basis of membrane permeability changes involved in drug and transmitter actions. The general areas studied include: cellular mechanisms regulating membrane excitability; cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin and GABA; membrane mechanisms of neurotransmitter, neurohormone and drug actions; cellular actions of enkephalin, endorphin and other neuropeptides; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbituates, opiates, and other neuroactive substances. Studies are performed primarily on *in vitro* preparations such as CNS slice, sympathetic ganglia, and tissue culture.

Studies of the molecular mechanisms involved in regulating neuronal excitability and membrane permeability employ physical techniques such as fluorescence absorption, polarization and lifetime, and biochemical methods such as gel electrophoresis, column chromatography, ligand binding, and high-voltage electrophoresis to identify, purify, characterize, and study membrane proteins. Studies include investigations on the role of protein phosphorylation, calcium ions, and cyclic nucleotides in the regulation of membrane properties.

National Institute of Allergy and Infectious Diseases

Richard M. Krause, M.D.,
Director
Kenneth W. Sell, M.D., Ph.D.,
Scientific Director
Michael M. Frank, M.D.,
Clinical Director

The National Institute of Allergy and Infectious Diseases (NIAID) annually appoints medical staff fellows for the laboratories described below. Fellows are selected by the clinical director, appointed to the Laboratory of Clinical Investigation, and begin after at least 1 year of residency training. Medical staff fellowship appointments in the other laboratories may begin after internship or residency training. In general, appointments to the Laboratory of Clinical Investigation carry responsibility for patients in the research program but are not otherwise different from those which begin after internship.

Specific answers to any questions or additional information may be obtained by applicants from the Scientific Director, NIAID, National Institutes of Health, Bethesda, MD 20205. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests and information desired.

Clinical Branches

Laboratory of Clinical Investigation—
Michael M. Frank, M.D.
Laboratory of Immunoregulation—
Anthony S. Fauci, M.D.

The NIAID appoints about 9 medical staff fellows. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned primary clinical responsibilities are made during the second or third year except as directed by the needs of the fellows' research.

There are 52 research beds. Medical staff fellows consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each fellow selects an area of investigative interest under the general preceptorship of the clinical director and the senior members of the staff of the Laboratory of Clinical Investigation or the Laboratory of Immunoregulation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in clinical investigation. Depending upon the area in which the medical staff fellow works, the subspecialty boards in infectious diseases or allergy-clinical immunology will usually credit the training received towards admission to these board examinations. Two to three staff fellows will be assigned to the Laboratory of Immunoregulation and six to seven to the Laboratory of Clinical Investigation.

Opportunities exist for research in a wide variety of areas of infectious, allergic, and immunological disease. Examples of studies now in progress are:

- The etiology, pathogenesis, and treatment of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases and vasculitis.

- Pathophysiology and treatment of autoimmune hemolytic anemia.
- Pathophysiology and treatment of hereditary angioedema.
- The pathophysiology and host defense response to bacteremia.
- Etiology and pathogenesis of the idiopathic hypereosinophilic syndrome.
- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- Mechanisms of regulation of immune reactivity in normal individuals and in patients with immunologically mediated diseases.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The biochemical, neurophysiologic, and immunologic abnormalities of asthma and allergic diseases.
- The role of immune complexes in the production of disease.
- Immunopathologic mechanisms in parasitic infections.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Laboratory and clinical evaluation of antiviral substances.

Further information can be obtained if inquiries with specific questions are addressed to Kenneth W. Sell, M.D., Ph.D., Scientific Director.

Research Areas and Senior Staff
Allergic Diseases—
Michael A. Kaliner, M.D., and
Dean Metcalfe, M.D.
Bacterial Diseases—
John I. Gallin, M.D.
Clinical Immunology—
Michael M. Frank, M.D.,
Eric Brown, M.D., and
Keith Joiner, M.D.
Clinical Mycology—
John E. Bennett, M.D.
Clinical Parasitology—
Franklin A. Neva, M.D.,
Eric A. Ottesen, M.D., and
Theodore Nash, M.D.
Immunoregulation—
Anthony S. Fauci, M.D.
Medical Virology—
Stephen Straus, M.D.
Mucosal Immunity—
Warren Strober, M.D.

Basic Research Laboratories

Laboratory of Viral Diseases—
Bernard Moss, M.D., Ph.D.

The Laboratory of Viral Diseases investigates the biological and molecular aspects of acute and chronic viral infection. Interest ranges from basic studies on the mechanism of gene expression and DNA replication to the natural history and epidemiology of tumor viruses. Areas of active research include the genetic engineering of DNA viruses as eukaryotic expression vectors and for use as novel, live recombinant vaccines, mapping and sequence analysis of viral genes and their regulatory elements, and *in vitro* synthesis of RNA and DNA. Pox viruses provide an important model system for the latter studies.

Research on the biology of murine leukemia viruses focuses on the genetics of transmission and expression of endogenous viral genomes, the biochemical nature of complete and incomplete endogenous viral genomes and their role in tumorogenesis. The latter studies include investigation of the interactions between defective and competent viruses. The natural history and epidemiology of tumor viruses, and the viral in host genetic factors of importance in viral tumorogenesis.

Research Areas and Senior Staff
Molecular Virology—
Bernard Moss, M.D.
Leukemia Viruses—
Janet Hartley, Ph.D.

Laboratory of Biology of Viruses—
Norman P. Salzman, Ph.D.

The investigations in this laboratory are primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein, and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for medical staff fellows is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology, and medicine.

Research Areas and Senior Staff
Biochemical Virology—
Norman P. Salzman, Ph.D.
Molecular Structure—
James A. Rose, M.D.

Laboratory of Infectious Diseases—
Robert M. Chanock, M.D.

This laboratory's activities are concerned with the basic behavior of viral and mycoplasmal pathogens that play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract and gastrointestinal tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as coronaviruses, acute gastroenteritis viruses, and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycoplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease, and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff
Epidemiology—
Albert Z. Kapikian, M.D.
Hepatitis Virus—
Robert H. Purcell, M.D.
Molecular Viral Biology—
Ching-Juh Lai, Ph.D.
Respiratory Viruses—
Robert M. Chanock, M.D.

Laboratory of Immunogenetics—
Thomas J. Kindt, Ph.D.

This group is involved in basic research on major gene complexes involved in immune function. The approaches used in these studies emphasize structural, serologic, and genetic investigations. The techniques used include quantitative radioimmunoassays, protein structure determinations, recombinant DNA technologies including gene cloning and nucleotide sequencing, preparation and study of T- and B-cell hybridomas, and a variety of immunologic assays for cellular and humoral components of the immune response.

Areas of active investigation include: studies on cloning, sequencing, and genetic analyses of genes for rabbit immunoglobulins and MHC products; structural and functional studies on murine H-2 antigens and human HLA antigens with emphasis on the D/DR complex; regulation of immunoglobulin gene expression during maturation of lymphocytes; use of hybridoma antibodies to investigate components of lymphoid cell membranes; and evaluation of the role of the MHC in the control of responses to individual antigens or infectious agents.

The opportunity is available for medical staff fellows to study in any of these areas under the preceptorship of a senior laboratory member. During their tenure, appointees become proficient in modern techniques of structural biochemistry and molecular biology and in quantitative and qualitative immunologic procedures. In addition, they gain an understanding of the genetic mechanisms underlying the ability to mount an immune response.

Research Areas and Senior Staff
Immunoglobulin Genetics—
T. K. Kindt, Ph.D., and
J. A. Sogn, Ph.D.
Membrane Antigens—
J. E. Coligan, Ph.D.
Molecular Immunogenetics—
E. E. Max, M.D., Ph.D.

Laboratory of Immunology—
William E. Paul, M.D.

This laboratory is engaged in the study of various aspects of cellular immunology, immunogenetics, and immunochemistry, particularly as they bear on a fuller understanding of the biological significance of the immune response and on the role of immune mechanisms in the prevention and pathogenesis of human disease.

Areas of active investigation include the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic and idiotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells. Studies of the role of different lymphocyte classes in many human diseases are under way, and models for the study of cellular immune responses in tumor immunity are being developed. Utilization of many modern techniques in the study of immune responses will be made, including production and use of monoclonal antibodies, cloning and long-term growth of B- and T-lymphocyte lines, and molecular genetic analysis of cells of the immune system. Medical staff fellows will have the opportunity to participate in studies in one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff
Cellular Immunology and Genetic Regulation of the Immune Response—
Ira Green, M.D., William E. Paul, M.D.,
Ronald H. Schwartz, M.D., Ph.D., and
Ethan H. Shevach, M.D.
Molecular Immunology and Immunogenetics—
Ronald N. Germains, M.D., and
Rose G. Mage, Ph.D.

Laboratory of Microbial Immunity—
Richard Asofsky, M.D.

The laboratory is primarily concerned with the elucidation of basic mechanisms involved in immune responses to microbial antigens.

Several major areas of investigation, each employing a wide variety of immunologic methods, offer the medical staff fellows comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. The development, distribution, and susceptibility of the interacting components to various treatments that suppress or amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations.

Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

Research Areas and Senior Staff

Experimental Pathology—
Richard Asofsky, M.D., and
Thomas Chused, M.D.
Microbiology and Immunology—
Phillip J. Baker, Ph.D.

Laboratory of Parasitic Diseases—
Franklin A. Neva, M.D.

This group of scientists is engaged in both basic and applied studies of parasitic diseases, with emphasis on those affecting man. A variety of protozoan (malaria, trypanosomes, giardia, leishmania, amebae, and toxoplasma) and helminth (schistosomes, filaria, and strongyloides) parasites are used for experimental work. Current studies include comparative mechanisms of energy transfer, ultrastructure of parasites, and host-parasite interactions *in vitro* and *in vivo*.

Increasing emphasis is being devoted to the immunologic response of the host in parasitic infections, both humoral and cellular. Another area of emphasis concerns the biochemical and immunologic characteristics of parasite surfaces and their interactions with the host cell membrane. Some experimental infections such as leishmaniasis, amebiasis, schistosomiasis, and filiarisis in animals are used as models of naturally occurring disease in man. The availability of different species of human as well as simian malaria parasites, an insectary, and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate, certain problems that can only be investigated in the field are studied in collaboration with institutions overseas. Clinical investigators from the Laboratory of Parasitic Diseases are associated with the Laboratory of Clinical Investigation within the Section of Clinical Parasitology. Thus, selected patients are seen and studied as inpatients or outpatients at the Clinical Center.

Within limits of space and available guidance by a member of the senior staff, medical staff fellows can select their area of work and a preceptor. In addition, an organized program provides medical staff fellows with an exposure to clinical parasitology.

Research Areas and Senior Staff

Host-Parasite Relations—
A. W. Cheever, M.D.
Cell Biology and Immunology—
F. A. Sher, Ph.D.
Clinical Parasitology—
F. A. Neva, M.D.,
T. E. Nash, M.D., and
E. A. Ottesen, M.D.
Malaria—L. H. Miller, M.D.
Parasite Growth and Differentiation—
L. S. Diamond, Ph.D.
Physiology and Biochemistry—
E. C. Weinbach, Ph.D.

Laboratory of Molecular Microbiology—
Malcolm A. Martin, M.D.

This laboratory uses molecular biological techniques to study microorganisms and their capacity to produce disease in vertebrate hosts. Of prime importance is the biochemical characterization of viral, bacterial, and plasmid genomes and the detailed analysis of DNA segments that regulate the expression of specific gene products.

Programs involving DNA and RNA tumor viruses focus on those portions of the viral genome that encode proteins that initiate and/or maintain the transformed state. The roles of the host cell genetic apparatus and the immunologic system in augmenting the effect(s) of specific viral gene products during oncogenesis are also investigated. Other programs investigate the process of bacterial transformation with special emphasis on the role of plasmids in transferring genetic information from one organism to another.

Biochemical and biophysical techniques, such as molecular cloning, nucleic acid hybridization, and DNA sequencing, are used in combination with procedures such as monoclonal antibody production and immunoprecipitation to answer basic questions involving the structure and function of prokaryotic and eukaryotic genes.

Research Areas and Senior Staff
Biochemical Virology—
Malcolm A. Martin, M.D.
Bacterial Virulence—
Donald LeBlanc, Ph.D.
Mycoplasma—
Joseph G. Tully, Ph.D.

Rocky Mountain Laboratories—
The Rocky Mountain Laboratories, located at Hamilton, Montana, consist of the following:

Laboratory of Persistent Viral Diseases—Bruce W. Chesebro, M.D.

This group is concerned with studies of virus-host interaction with the primary aim of elucidating mechanisms involved in establishment, maintenance, and elimination of persistent viral infections. Investigations are also made on involvement of persistent virus infection and autoimmune and immune complex diseases. Appropriate models being examined include rabies virus, scrapie, murine leukemia viruses, and Aleutian disease virus of mink.

Research Areas and Senior Staff
Murine Leukemia Viruses—
Bruce Chesebro, M.D., and
John Portis, M.D.
Aleutian Disease Virus—
Marshall Bloom, M.D.
Scrapie—
Richard Race, D.V.M.
Rabies—
Donald Lodmell, Ph.D.
Immunology—
John Coe, M.D.

Laboratory of Microbial Structure and Function—John Swanson, M.D.

Bacteria pathogenic for man are the major topics for study in this laboratory. Special attention is paid to surface components of selected bacteria, rickettsiae, mycoplasmas, and chlamydiae that relate to the virulence and/or pathogenicity of these organisms. In addition to biochemical and immunochemical studies of these organisms' surface constituents, current studies also include investigation of the metabolic capabilities and characteristics of selected rickettsial agents, toxin and other products of staphylococci and *Bordetella pertussis,* and genetic control or expression of these bacterial elements. The general goal of these studies is to document, characterize, and understand interactions between pathogenic prokaryotes and cellular or humoral components of the infected host so mechanisms of pathogenicity and virulence can be elucidated.

Research Areas and Staff—
Borrelia—
Alan Barbour, M.D.
Chlamydia—Harlan Caldwell, Ph.D.
Gonococci—
John Swanson, M.D.

Epidemiology Branch—
Willy Burgdorfer, Ph.D.

The staff of this branch plans and conducts epidemiologic investigations and studies on natural histories of human diseases. One research group performs surveillance of arthropod-borne agents of human disease importance. Another group undertakes detailed histopathologic investigations of naturally occurring diseases in animals, naturally occurring slow viral diseases of animals, and infectious problems in animal models which may be related to findings in counterpart diseases of man.

Research Areas and Senior Staff

Arthropod-borne Diseases—
Willy Burgdorfer, Ph.D.
Histopathology—
William Hadlow, D.V.M.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Lester B. Salans, M.D.,
Director
Jesse Roth, M.D.
Director of Intramural Research
Phillip Gorden, M.D.,
Clinical Director

Appointments in Clinical Research

Each medical staff fellow is assigned to one of the Institute's clinical branches or sections, which he or she carries out both clinical work and laboratory studies. The fellow is, in effect, an apprentice investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The fellow is encouraged to choose his or her own problem for independent investigation, if facilities, technical advice, and supervision are available. In addition, the fellow provides professional care for research patients admitted to the service of the branch chief and assists in the outpatient department. There is considerable variation among the branches of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) with respect to the proportion of the fellow's time required for patient care activities.

Medical staff fellows of the Clinical Endocrinology, Diabetes, and Metabolic Disease branches participate in a 3-year Interinstitute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIADDK fellows may spend a third year in the Endocrinology Program.

The Institute recruits about 10 new medical staff fellows each year. The assignments are for 2 or 3 years and usually are not extended. One year of internship and at least one year of residency should generally be completed before the appointment begins.

Vacancies do not necessarily occur within each program each year; the Program Area Selection Checklist indicates the positions to be filled. The chiefs of branches or sections with openings and the clinical director screen applications and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical research branches are listed below with the names of the permanent investigators and a brief sketch of the areas of interest. Prospective applicants desiring more information should write to Phillip Gorden, M.D., Clinical Director, NIADDK, Building 10, Room 9N222, National Institutes of Health, Bethesda, MD 20205. Supplementary information sheets on each branch, together with selected bibliographic citations are available on request.

Appointments in Laboratory Research

NIADDK has four positions in laboratory research available each year for medical staff fellows. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During their stay here, fellows will devote the larger part of their time to laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should candidates elect a clinical area, they would not participate in clinical care of patients. The medical staff fellow, approximately 1 year prior to beginning, will visit NIADDK to select the laboratory and preceptor with whom he or she wishes to work. Candidates desiring further information about the laboratories, staffs, and bibliography can obtain this by writing Jesse Roth, M.D., Director of Intramural Research, NIADDK, National Institutes of Health, Bethesda, MD 20205.

Developing Programs

Programs in clinical and basic research are being developed in NIADDK in the following areas: nephrology, nutrition, and cystic fibrosis. For further information, contact Jesse Roth, M.D., or Phillip Gorden, M.D., Building 10, Room 9N222, National Institutes of Health, Bethesda, MD 20205.

Medical Staff Fellows in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2-year assignment for studying the epidemiology of chronic disease such as diabetes and arthritis among the Pima Indians of Arizona. In addition, clinical research opportunities in the causes, complications, and treatment of diabetes are available at the Phoenix Clinical Research Section in the Phoenix Indian Medical Center. Most candidates complete post-doctoral training before beginning this fellowship. Occasionally, candiates begin the fellowship after completion of an internship. Candidates interested in clinical research are encouraged to write to Clifton Bogardus, M.D., Phoenix Clinical Research Section, 4212 N. 16th Street, Phoenix, Arizona 85016. Those interested in epidemiology should write Peter H. Bennett, M.D., Epidemiology and Field Studies Branch, NIADDK, 1550 E. Indian School Road, Phoenix, Arizona 85014, for more detailed information.

Clinical Research Branches

Arthritis and Rheumatism Branch—
Henry Metzger, M.D.

- Section on Connective Tissue Disease—Henry Metzger, M.D., James E. Balow, M.D., John H. Klippel, M.D., Paul H. Plotz, M.D., and Ronald L. Wilder, M.D., Ph.D.

The pathogenesis of systemic lupus erythematosus and rheumatoid arthritis is under study both in patients with those diseases and animal models. The role of immune complexes, reticuloendothelial function, *in vitro* and *in vivo* lymphocyte and monocyte function, and various other aspects related to the immunopathogenesis of these diseases are under active study. Clinical work is related to the development of new forms of treatment of lupus, especially with nephritis, and severe rheumatoid arthritis, including new pharmacologic and cytopheretic techniques.

- Section on Cellular Immunology—Alfred D. Steinberg, M.D.

The section conducts studies on the genetic and immune bases for autoimmune diseases in mice and humans with emphasis on systemic lupus erythematosus.

- Section on Chemical Immunology—Henry Metzger, M.D., and Chaviva Isersky-Carter, Ph.D.

The section is involved in fundamental research on the structure and mechanism of immunoglobulins and their receptors on cells, using protein chemistry, immunochemistry, tissue culture, and electron microscopy techniques.

Clinical Endocrinology Branch—
Jacob Robbins, M.D., Jan Wolff, M.D., Ph.D., Saul Rosen, M.D., Ph.D., Harold Edelhoch, Ph.D., and Bruce Weintraub, M.D.

Activities in this branch range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid and polypeptide hormones. Laboratory research encompasses fundamental and applied protein chemistry, including studies on hormone transport proteins and polypeptide hormones, the mechanism of hormone actions, control mechanisms in secretory cells, adenylate cyclase-receptor interactions and membrane biochemistry, and the biosynthesis of polypeptide hormones.

Clinical Hematology Branch—
N. Raphael Shulman, M.D.

Laboratory work concerns problems in the fields of immunohematology, platelet physiology and metabolism, and blood coagulation. Current interests include mechanisms of immune platelet injury involving drug-, allo-, and so-called autoantibodies, correlation of platelet metabolism and membrane reactions with function, and interrelationships between cellular and humoral factors in hemostasis. Clinical work involves patients with immunologic and hemorrhagic disorders relevant to laboratory studies.

Diabetes Branch—
Phillip Gorden, M.D., Jesse Roth, M.D., Simeon Taylor, M.D., Ph.D., and Derek LeRoith, M.D., Ph.D.

The Diabetes Branch studies receptors for peptide hormones, especially insulin, insulin-like growth factors, and growth hormone. Current projects are focused on the role of receptors in disease states, receptor antibodies, and genetic disorders of glucose metabolism, isolation and characterization of receptor components, the role of receptors in hormone and drug action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects include insulin and insulin receptors in the central nervous system; the evolutionary origin of insulin, somatostatin, an other peptide messenger molecules; and their role in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

Digestive Diseases Branch—

- Section on Gastroenterology—
  Jerry D. Gardner, M.D., and
  Robert T. Jensen, M.D.

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive and immunologic processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology, biochemistry, and immunology.

- Liver Diseases Section—
  E. Anthony Jones, M.D., and
  Jay H. Hoofnagle, M.D.

Programs are concerned with research into hepatic physiology, immunology, and disease. Laboratory research projects include studies of cellular immunology and the modulation of immune responses in primary biliary cirrhosis and other chronic liver diseases; investigations of the significance of various viral antigens and antibodies in chronic type B hepatitis, characterization of cell-surface receptors on isolated hepatocytes, Kupffer cells, and hepatic endothelial cells; and the evaluation of the pathogenetic mechanisms that mediate the encephalopathy in an animal model of fulminant hepatic failure. Clinical investigations include studies of the natural history of chronic type B hepatitis and chronic non-A, non-B hepatitis, evaluations of the efficacy of antiviral agents in the treatment of chronic type B hepatitis, and a controlled trial of immunosuppressive therapy in primary biliary cirrhosis.

Genetics and Biochemistry Branch—
Elizabeth F. Neufeld, Ph.D.

- Biochemical Genetics Section—
  Elizabeth F. Neufeld, Ph.D.
- Molecular Genetics Section—
  R. Daniel Camerini-Otero, M.D., Ph.D.

The branch conducts studies in biochemical and molecular genetics. The range of current projects covers a wide field from the very basic (*e.g.,* mechanisms of genetic recombination and gene conversion in mammalian cells, DNA-mediated gene transfer, biosynthesis and transport of lysosomal proteins and the biochemical and molecular bases of human genetic disorders) to the more applied (development of new diagnostic tests and carrier detection for a number of genetic diseases, preparation of enzymes for replacement therapy, and the development of new techniques for gene purification and transfer).

Laboratory of Chemical Biology—
Alan N. Schechter, M.D.

The clinical focus of this section is on the pathophysiology of the hemoglobinopathies and other red cell diseases. Basic studies are concentrated on using NMR, cell separation and molecular genetic techniques to examine molecular interactions and metabolic processes in normal and sickle erythrocytes and erythroid cells. Several clinical protocols are designed to develop non-invasive methods, including laser-Doppler velocimetry, PET and other imaging modalities, to assess the severity of sickle cell anemia and to follow the results of therapy. The section participates in the NIH Interinstitute Clinical Genetics Program. (For non-clinical studies see Basic Research Laboratory listing.)

Metabolic Diseases Branch—
Gerald D. Aurbach, M.D.,
Stephen J. Marx, M.D., and
Allen M. Spiegel, M.D.

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, parathyroid hormone, and calcitonin. The clinical program involves studies of patients with disorders of mineral metabolism. These include patients with hereditary resistance to parathyroid hormone or to calciferols. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is used for *in vitro* studies on control of hormone secretion.

Phoenix Clinical Research Section—
Clifton Bogardus, M.D.,
Barbara V. Howard, Ph.D.,
Lester B. Salans, M.D.,
and Peter H. Bennett, M.B.

This section is currently involved in studies of diseases particularly prevalent among southwestern American Indians. One of the major areas under investigation is diabetes mellitus in the Pima Indian population. This group has the world's highest reported prevalence of type II (noninsulin dependent) diabetes. The geographical proximity of this unique population to the Phoenix area provides an excellent opportunity for insight into the causes and complications of type II diabetes. A problem closely related to the diabetes in this group is that of obesity. These areas are under intensive scientific investigation in both the 24-bed clinical research unit and the basic science research laboratory which are co-located within the Indian Health Service Referral Hospital, Phoenix, Arizona.

Clinical studies currently in progress include whole-body insulin resistance, nutrition-induced alterations in metabolism, lipid and lipoprotein metabolism, and dietary and exercise therapy in the treatment of diabetic patients. The laboratory research is centered around insulin-mediated glucose metabolism in adipocytes from diabetic and nondiabetic donors, fat cell metabolism, as well as a variety of studies supporting the clinical investigations.

Close collaboration with the Epidemiology and Field Studies Section allows investigation into the prevalence of not only diabetes and obesity, but also cardiovascular disease, gallbladder disease, lipid and lipoprotein abnormalities, and rheumatoid arthritis in the Pima Indians.

Basic Research Laboratories

Laboratory of Biochemical Pharmacology—Herbert Tabor, M.D.,
Simon Black, Ph.D.,
Anthony Furano, M.D.
Victor Ginsburg, Ph.D.,
Leonard D. Kohn, M.D.,
Nancy Nossal, Ph.D., and
Reed B. Wickner, M.D.

The work of this laboratory includes a large variety of biochemical, genetic, and molecular biological investigations. Included are studies on polyamine synthesis and action, nucleic acid and protein biosynthesis, tryptophan biosynthesis, and yeast and *Escherichia coli* genetics. Studies are also carried out on developmental biology and genomic structure and aim at identifying and isolating those genes that must be expressed to attain or maintain a particular state of cell differentiation.

One section is concerned in particular with the structure, function, and bioenergetics of biological membranes and the mechanism by which various effectors—hormones, toxins, neurotransmitters, interferon, and viruses—transmit their information through these members to the interior of the cell. Another subsection studies diverse aspects of the related hormones insulin and somatomedin, including: structure, biosynthesis, mechanism of action, biological role, and genetic syndromes of hormone resistance.

A third section is concerned with the biology and immunology of the complex carbohydrates of animal cell surfaces.

A fourth section is studying the genetic control of replication of a double-stranded RNA virus of yeast and other problems in the genetics of simple eukaryotes.

Laboratory of Biochemistry and Metabolism—
G. Gilbert Ashwell, M.D.,
William B. Jakoby, Ph.D., and
Yale J. Topper, Ph.D.

The laboratory program is directed toward an understanding of the basic biochemical mechanisms involved in both normal and abnormal biological processes. Within this general framework, independent projects cover a broad range of biochemical investigations.

A brief summary of the major areas under study includes an examination of the hormone-dependent differentiation and development of mammary gland tissue in normal and hypophysectomized rats; a detailed study of growth and development whereby the formation of the primary septum of yeast is used as a molecular model for morphogenesis; studies on the mechanism of receptor-mediated endocytosis and glycoprotein-membrane sorting in eukaryotes; and a study of the cluster of enzymatic activities classified as enzymes of detoxication that function in the conjugation of foreign compounds in mammals and the role of cellular factors involved in the biosynthesis and differentiation of lymphocytes in spleen and thymus. In addition to the above general areas, specific projects of individual investigators include a study of the particulate enzymes involved in carbohydrate metabolism, biochemical abnormalities in human cystinosis, genetic control of bacterial membrane proteins, and thermodynamic and kinetic studies on enzymatic mechanisms.

Laboratory of Bioorganic Chemistry—
John W. Daly, Ph.D., and
Donald M. Jerina, Ph.D.

This laboratory's research mission is to elucidate the mechanism of interaction of pharmacologically active substances with biological systems. Research is designed toward the development of new chemical agents as tools for the study of membrane and cytosol functions of cells. New mechanisms of action or metabolism of such agents are also investigated for their potential use as therapeutics. Development and application of modern techniques of organic chemistry for the synthesis, separation, and spectral investigation of these chemical agents and their interactions with macromolecules are emphasized. The goal is to provide insights into the normal and pathologic function of biological systems and to delineate the metabolic formation, fate, and action of physiologically active agents such as amino acids, biogenic amines, cyclic nucleotides, hormones, neurotransmitters, and steroids. Studies include pharmacologically active agents such as natural products, therapeutic agents, toxins, carcinogens, and mutagens.

Laboratory of Chemical Biology—
Alan N. Schechter, M.D., and
Hiroshi Taniuchi, M.D., Ph.D.

Research in this laboratory is concerned with structure-function relationships in macromolecules. Dr. Schechter and his group are studying the control of hemoglobin synthesis, using molecular genetic techniques in cultured human erythroid cells. The work includes analyses of cloned globin genes and transfecting heterologous genes into erythroid cells. In addition, biophysical methods, especially NMR spectroscopy, are being used to study molecular interactions inside erythrocytes, including the polymerization of sickle hemoglobin. Dr. Taniuchi and his colleagues are studying the folding and dynamics of proteins, using cytochrome *c* as a model, with a variety of chemical and physical techniques, including peptide synthesis and NMR. A project on the dyanmics of antibody specificity has been initiated. Other projects in the laboratory include study of neurophysin-neuropeptide interactions and neurophysin biosynthesis, affinity chromatography and blood platelets.

Laboratory of Chemical Physics—
Edwin D. Becker, Ph.D., Elliot Charney, Ph.D., William A. Eaton, M.D., Ph.D., William A. Hagins, M.D., Ph.D., and Ira W. Levin, Ph.D.

Research in this laboratory is characterized by the application of modern physical techniques to the study of a wide range of biological problems. Among the current research interests of the staff are: analysis of the kinetics and mechanism of aggregation of hemoglobin-S, study of the association of mononucleotides and of the conformational behavior of polynucleotides, investigations of the excitation of visual photoreceptors and resultant ionic processes in membranes, analysis of excited electronic states of small molecules in the vapor phase and in molecular beams, development of methods for asymmetric synthesis, study of the structural characteristics of model membrane systems, the structure and dynamic behavior of nucleic acids and nucleoproteins, and the dynamics of ligand binding and structural changes in hemoglobin. Much of the research involves the use of a variety of spectroscopic methods—for example, nuclear and electron magnetic resonance, laser-Raman and resonance Raman spectroscopy, electric-field-induced dichroism, ultraviolet and visible microspectrophotometry, and time-resolved absorption spectroscopy with nanosecond lasers.

Laboratory of Chemistry—
Bernhard Witkop, Ph.D., Sc.D., Louis A. Cohen, Ph.D., Arnold Brossi, Ph.D., Cornelius P. J. Glaudemans, Ph.D., and David F. Johnson, Ph.D.

In the oldest laboratory of the Institute (founded June 20, 1905), chemistry is represented in its broadest context in five independent sections investigating the mechanisms of enzymatic reactions and their simulation, medicinal chemistry, steroid hormones, immunochemistry, novel toxins, metabolism, antiviral agents, interferon, and analysis and instrumentation. Some of the recent achievements concern the role of retinoids in bladder cancer, effects of novel colchicine derivatives on microtubules, affinity labeling of glucocorticoid receptors, separation of addictive from analgesic properties in new synthetic morphine substitutes, characterization of sodium channels in electrogenic membranes by a frog toxin, the acetylcholine receptor, development of fluorinated amino acids and biogenic amines as selective probes and inhibitors of enzymatic and metabolic processes, hypoxic cell sensitizers, cytotoxic agents selective for cancer cells, the interaction between antigens and monoclonal antibodies, recombinant hybrid immunoglobulins and the detailed structure of fungal antigens, and chemistry and biochemistry of interferon induction and interferon-related enzymes.

Laboratory of Cell Biology and Genetics—
Harvey B. Pollard, M.D., Ph.D.
Barrie J. Carter, Ph.D., Loretta Leive, Ph.D., Ned Feder, M.D., and Joe-Hin Tjio, Ph.D.

The laboratory carries out basic studies and collaborative clinical studies relating to secretion of hormones and transmitters from nerve and endothelial cells. Other work includes analysis of endocytosis and phagocytosis by macrophages and macrophage cell lines, structure of nerve and other cell types by both light and electronmicroscopy, immunology and cytogenetics of autoimmunity, and of the molecular biology of viral genomes.

Laboratory of Molecular Biology—
Martin Gellert, Ph.D., Jun-ichi Tomizawa, Ph.D., Gary Felsenfeld, Ph.D., David R. Davies, Ph.D., Robert Martin, Ph.D., H. Todd Miles, Ph.D., and Terrell Hill, Ph.D.

The work of the laboratory is concerned with understanding biological processes in terms of structure and reaction at the molecular level. Research includes direct investigations of biological processes, such as genetic recombination, DNA replication, and protein synthesis, studies of the mechanism of transformation by SV40 (a virus causing tumors in hamsters), and studies of the mechanism of hemoglobin S gelation, the phenomenon that causes sickling of red blood cells in sickle cell anemia. Other investigations are concerned with the structure and chemical properties of biologically important materials. These include studies of the organization of DNA and proteins in chromatin, investigations of protein structure by X-ray diffraction and of nucleic acid and polynucleotide structure by diffraction and spectroscopic methods, and theoretical studies of the mechanisms of free energy transduction, muscle contraction, membrane properties, and biochemical kinetics.

Laboratory of Cellular and Developmental Biology—
Robert T. Simpson, M.D., Ph.D.,
Martin Rodbell, Ph.D.,
Bernard T. Kaufman, Ph.D., and
Robert O. Scow, M.D.

This laboratory consists of four sections devoted to various biochemical and physiological investigations. The Section on Endocrinology investigates hormonal regulation of enzymes involved in chylomicron uptake and metabolism in adipose and mammary tissues, the influence of hormones on cellular development and metabolism, and the disposition of fat and metabolites in the cell as viewed from ultrastructural studies. The Section on Nutritional Biochemistry investigates the structural and functional aspects of dihydrofolic reductase and other enzymes involved in folic acid metabolism and the intermediary metabolism of lipids, carbohydrates, and amino acids in the small intestine. The Section on Membrane Regulation studies the mechanism of action of hormones on adenylate cyclase and other membrane regulatory processes. The Section on Developmental Biochemistry investigates the structure and function of chromatin and the regulation of gene function during development.

Laboratory of Physical Biology—
R. J. Podolsky, Ph.D., and J. Buck, Ph.D.

This laboratory carries out a broad range of studies. The mechanism of muscle contraction is studied in intact cells and in simplified preparations, using time-resolved X-ray diffraction in conjunction with mechanochemical techniques. Activation of muscle cells is examined by measuring calcium movement between the myofilaments and the sarcoplasmic reticulum in skinned muscle fibers. Lipid dispersions in water are investigated as models of the structure and physical states of lipids in cell membranes. The actions of ionizing radiation on macromolecules are used to determine the *in vivo* size of the functional units for different biological activities (hormone receptors, enzyme complexes, and regulatory units). Electron microscopy is carried out with a wide variety of preparations, and digital image processing techniques are used to enhance resolution. Other subjects under investigation are enzyme organization in unicellular organisms, metamorphosis in insects, human red cell sickling, and biological rhythms and entrainment.

Mathematical Research Branch—
John Rinzel, Ph.D.

The branch conducts research on the mathematical and theoretical aspects of biological problems and the development of analytical and numerical methodology underlying such an approach. The research programs are designed to provide a formal basis and theoretical apparatus for the rational analysis and quantitative interpretation of biological phenomena. *Research is organized around biological subject-matter areas rather than around subdisciplines of mathematics.* Major research topics include transport and consumption of substrates at the tissue-capillary level, electrotonus in neuronal dendritic systems, excitability and auto-rhythmicity in neuroelectric signaling, bifurcation, and stability studies of nerve conduction and diffusion-reaction systems, nonlinear chemical/biochemical oscillations, analysis of nucleic and amino acid sequences, and mathematical modeling of renal functions.

National Institute of Child Health and Human Development

Mortimer B. Lipsett, M.D.,
Director
Arthur S. Levine, M.D.,
Scientific Director, (Director, Intramural Research)
D. Lynn Loriaux, M.D., Ph.D.,
Clinical Director

The Intramural Research Program is broadly concerned with the biological and neurobiological, medical, and behavioral aspects of normal and abnormal human development. In addition to four major clinical research and training programs in the areas of genetics and endocrinology, a diversity of developmental models are under study in eleven fundamental research laboratories, drawing upon observations in bacteria, *Drosophila,* yeasts, viruses, molluscs, frogs, rodents, and subhuman primates. Disciplines employed in these studies include biochemistry, virology, molecular biology, immunology, pharmacology, genetics, cell and neuronal biology, biophysics and theoretical biology, reproductive physiology and developmental psychology.

Each medical staff fellow will devote time mainly to research in the laboratory under the supervision of a senior preceptor. Each is expected to engage in appropriate course work in the basic and/or medical sciences as well as tutorial seminars, and to take an active part in the journal club, lecture series, and other laboratory exercises.

All appointments as medical staff fellows are for a minimum of 2 years with a third optional year. Most fellows elect to remain for 3 full years and are offered this opportunity. For a limited number of highly qualified fellows, additional years of training are possible.

The Intramural Research Program's eleven branches and laboratories are each under the direction of a branch or laboratory chief. Medical staff fellow positions are usually available in all of these areas. The fellows have an exceptional opportunity to become independent scientists in a field of their interest, and to prepare themselves for a career in academic medicine and research.

Prospective applicants wishing further information should write to Arthur S. Levine, M.D., Scientific Director, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20205. In writing, please be specific as to your interests and the information you require.

Appointments in Clinical Research

These appointments are designed to give physicians training in both clinical and basic research.

Medical staff fellows will be responsible, under the guidance of senior investigators on the NICHD staff, for the primary medical care of research patients during the first year of their service. During this time, they will serve in the medical services that are associated with the clinically oriented branches of the Institute and assist in the work of the service with inpatient care, consultation and in the outpatient department. The clinical period offers exposure to rich case material and to highly sophisticated approaches to clinical investigation.

The fellow devotes the subsequent time to laboratory research under direction of a senior preceptor in any one of the eleven Institute laboratories. The choice of laboratory is made during the fellow's first 6 months at NIH. No clinical responsibilities are required during the second or additional years for fellows who have chosen nonclinical laboratories.

The NICHD selects nine medical staff fellows each year who participate in one of the four approved clinical subspecialty training programs sponsored by this Institute: adult endocrinology, pediatric endocrinology, gynecologic endocrinology, and medical genetics.

Fellows in adult endocrinology apply to the Developmental Endocrinology Branch and participate in the NIH Joint (inter-institute) Endocrinology Fellowship Program which leads to board certification by the American Board of Internal Medicine in the subspecialty of endocrinology and metabolism (see page 5). Applicants must be board eligible in the specialty of internal medicine prior to the initiation of the fellowship. The first year of the fellowship is primarily clinical. Further years are devoted to a research project which may be carried out in any of the eleven branches or laboratories of the NICHD.

Applicants for the pediatric endocrinology fellowship also apply to the Developmental Endocrinology Branch and must have completed PL-3 level training prior to the initiation of the fellowship. The first year is primarily clinical, with pediatric patient care responsibilities in the three endocrinology units associated with the NIH Joint Endocrinology Fellowship Program. The further years are spent in any one of the branches or laboratories of NICHD. This fellowship is approved by the American Board of Pediatrics and leads to board certification in the subspecialty of pediatric endocrinology.

Applicants for the gynecologic endocrinology fellowship apply to the Office of the Scientific Director and must have completed an accredited residency in obstetrics and gynecology prior to the first fellowship year. The fellowship is a cooperative program utilizing the combined clinical facilities of the NIH, the National Naval Medical Center, and the Walter Reed Army Medical Center. The first year is entirely clinical, 6 months being spent on the combined endocrine services of the NIH, and 6 months in the infertility clinics of the two Service hospitals. The following years of the fellowship are spent in a research program that may be undertaken in any of the branches or laboratories of the NICHD. This program is recognized by the American Board of Obstetrics and Gynecology and leads to certification in the subspecialty of gynecologic endocrinology.

Fellows in medical genetics apply to the Human Genetics Branch and participate in the NIH Interinstitute Medical Genetics program (see page 6). The program fulfills all of the requirements proposed by the American Board of

Medical Genetics and leads to board certification in this subspecialty. Candidates may be pediatricians or internists, and occasionally represent other medical specialties such as neurology and obstetrics. As with the other NICHD clinical specialty programs, the first year of the fellowship is primarily clinical, with patient care responsibilities on the research wards, in the NIH, Johns Hopkins, and Children's Hospital Genetics Clinics and in the NIH-supervised Prenatal Diagnosis Clinic at George Washington University Hospital. The further years are spent in a research program in any NICHD laboratory or branch of the fellow's choice.

Applications for all four of these programs are considered 1 or 2 years in advance of the proposed starting date. Application forms may be obtained from the NIH Medical Staff Fellowship office, Building 10, Room 2N220A, National Institutes of Health, Bethesda, Maryland 20205.

Appointments in Laboratory Research

A limited number of appointments are available which are designed to give highly qualified physicians an opportunity to do basic research in any area of the Institute under the direct supervision of a senior preceptor. Usually physicians enter the appointment after completing internship and at least 1 year of residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved, the fellows are welcome to attend any of the clinical teaching exercises. Fellows with this appointment work exclusively with the branch or laboratory in which they are accepted, and make this choice at the time of initial application.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Medical staff fellows are expected to take advantage of this academic work. (See page 133.)

Medical Staff Fellows in Pharmacology (PRAT)

Several of the NICHD laboratories and branches participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in preclinical or clinical pharmacology. For more information about the PRAT program see page 85.

Clinical Research Branches

Developmental Endocrinology Branch—
D. Lynn Loriaux, M.D., Ph.D., Chief

The endocrine concomitants of normal and abnormal human growth, development, and differentiation are examined in this branch. Specific areas of study include the mechanisms underlying the initiation of puberty; the regulatory physiology and biochemistry of the glycoprotein hormones; the roles of sex steroid hormones, growth hormones, and other growth factors in bone growth; and the physiology and biochemistry of the action of hypothalamic releasing hormones. Clinical research on male and female reproductive disorders is also a major interest of this branch.

- Section on Steroid Hormones—
  D. Lynn Loriaux, M.D., Ph.D.

The mechanism of action of the steroid hormones is under investigation, including studies of the clinical disorders of masculinization, feminization, and glucocorticoid deficiency or excess. In this regard, patients with polycystic ovarian disease, gynecomastia, polyendocrine deficiency, and Cushing's syndrome play an important role in the clinical research program of the branch. Two syndromes of resistance to steroid hormone action, testicular feminization and cortisol resistance, are under intensive study as well.

- Section on Developmental Endocrinology—
  Gordon B. Cutler, M.D.

This section studies the pathophysiology of the syndromes of precocious and delayed puberty and the treatment of these disorders, including the use of LHRH agonist analogues. The section also examines the role of sex steroid hormones in long bone growth, and is exploring the treatment of disorders of stature with agents such as sex steroids, growth hormone, and hypothalamic releasing hormones.

- Section on Medical Endocrinology—
  Bruce C. Nisula, M.D.

The glycoprotein hormones, TSH, LH, FSH, and hCG, are the subjects of both clinical and basic research studies, and understanding the physiology of regulation of TSH, LH, and FSH secretion by the pituitary is a major goal. The development of new diagnostic procedures involving the glycoprotein hormones and evaluation of their clinical applications are emphasized. Clinical disorders of thyroid function and conditions characterized by abnormal glycoprotein hormone secretion are being studied to elucidate the role of molecular heterogeneity in these situations. The regulation of thyroid function through the TSH receptor-adenylate cyclase system is of particular interest.

- Section on Reproductive Endocrinology—
  Richard J. Sherins, M.D.

Human reproduction is the major area of interest in this section. The hormonal control of gonadal development and the basic physiology of gametogenesis are investigated. Clinical investigations on the full range of male and female gonadal disorders, and especially infertility, are aimed at understanding pathogenetic mechanisms and developing new therapeutic modalities.

Human Genetics Branch—
Michael A. Zasloff, M.D., Ph.D.

The Human Genetics Branch's interests range from studies on the etiology, diagnosis, and treatment of genetic and developmental disorders of young people to very basic studies on eukaryotic gene expression utilizing recombinant DNA methodology. The intent of the branch's clinical fellowship program is to provide wide exposure to the field of human genetics, including clinical care, clinical research, and basic studies. Current research projects concern genetic disorders of lipid and carbohydrate metabolism, the mucopolysaccharidoses, heritable disorders of bone and connective tissue, lysosomal storage diseases (e.g., cystinosis), temperature-sensitive models of cellular differentiation, the genetics of alcohol-related syndromes, and the structure and function of human tRNA genes.

- Section on Cellular Differentiation—
  Janice Chou, Ph.D.

This section conducts research on the mechanisms of gene function and regulation during mammalian cell differentiation. Major emphasis is on the investigation of biochemical and molecular changes associated with normal and abnormal differentiation processes. Techniques utilized include tissue and organ culture, and recombinant DNA methodology.

- Section on Developmental Genetics—
  Anil Mukherjee, M.D., Ph.D.

This section emphasizes biochemical, cellular, and immunological studies on early mammalian development. Currently, basic and clinical studies are being conducted to understand the etiology of the fetal alcohol syndrome, as well as the genetic basic of ethanol intolerance in man. Techniques utilized include tissue culture and fetal studies on non-human primates.

- Section on Disorders of Carbohydrate Metabolism—
  James B. Sidbury, M.D.

This section focuses on the natural history, diagnosis, treatment and pathophysiology of genetic disorders of carbohydrate metabolism, with a special emphasis on obesity, galactosemia, and the glycogen storage disorders.

- Section on Biochemical Genetics—
  Michael A. Zasloff, M.D., Ph.D., Acting

A combination of clinical and laboratory-based research is used to identify the biochemical etiology of genetic diseases such as cystinosis, gluthathione defects, the mucopolysaccharidoses, and rare disorders of bone and connective tissue such as osteogenesis imperfecta and fibrodysplasia ossificans progressiva. Emphasis is also placed on the development of new methods of prenatal diagnosis, the detection of heterozygotes, and treatment.

- Section on Molecular Biology—
  Michael A. Zasloff, M.D., Ph.D.

This section studies basic mechanisms of eukaryotic gene expression as a means of understanding disease processes. Current studies include genomic organization and expression of human tRNA genes, the mechanism of nuclear RNA transport. Techniques utilized include recombinant DNA methodology, amphibian oocyte injection, and DNA transfer into somatic cells.

Laboratory of Comparative Ethology—
Stephen J. Suomi, Ph.D.

Research in this laboratory is focused on the development of behavior in humans, primates, and other animal models. The interactions of genetic and environmental factors are explored, using a comparative mammalian approach, so as to determine the origins and evolution of various behavioral phenotypes. Experimental results in animals are correlated with the results of longitudinal studies in human infants and families. At the same time, hypotheses concerning behavior in the animal models are correlated with results obtained by physiological and molecular neuroscience techniques.

- Section on Comparative Behavioral Genetics—
  Stephen J. Suomi, Ph.D.

This section studies genetic and environmental interactions through comparative ontogenic study of rhesus monkeys and other animals (living under seminatural conditions). The neuroanatomical, electrophysiological, and biochemical concomitants of various behavioral phenotypes are determined, as well as the development of cognitive abilities from birth through senescence. Monkeys bred to yield specific behaviors under stress (*e.g.*, ''laid back'' or ''uptight'') are used extensively.

- Section on Brain, Behavior and Communication—
  David Symmes, Ph.D.

The focus of interest is on vocal communication, learning, and play among subhuman primates and other animals, and the relationship of these behaviors to those of humans. The section analyzes the electrophysiologic correlates of sensory coding and discriminative behavior using microelectrode computer techniques, and also studies the behavioral consequences of nutritional deprivation or biochemical lesions of the central nervous system.

- Section on Child and Family Research—
  Frank A. Pedersen, Ph.D.

This section investigates early influences on the development of human behavior and personality. These studies are undertaken within the context of family and cultural structures, and factors in the home that influence cognitive and motivational development are being explored, such as the events surrounding childbirth, the infant's separation experiences, and maternal employment. All of these studies are longitudinal in design.

Basic Research Laboratories

Office of the Scientific Director—

- Section on Growth Factors—
  Gordon Guroff, Ph.D.

This section is studying the mechanism of action of growth factors of neurochemical interest, the biosynthesis and degradation of molecules in neural tissue, and the physiology of nerve growth factor. Other studies concern the evaluation of the effects of somatic growth factors on cellular differentiation and proliferation.

- Section on Viruses and Cellular Biology—
  Arthur S. Levine, M.D.

DNA viruses which influence differentiation are used to probe the developmental program of macromolecules (*e.g., onc* gene products) that regulate changes in the phenotypes of normal and transformed animal cells. The DNA viruses are also utilized as models in studies on the mechanics and kinetics of DNA replication. The techniques of virology, tissue culture, cell somatic hybridization, molecular biology, and immunology are employed.

- **Laboratory of Developmental Neurobiology—**
  Phillip G. Nelson, M.D., Ph.D.

The neurobiologic mechanisms relevant to development of the nervous system are investigated with emphasis on studies at the cellular membrane and molecular levels. The basis for short- and long-term interaction between nerve cells is studied electrophysiologically and biochemically. Combined molecular and morphological methods are used in the analysis of experiential modifications of brain function and gene expression.

- Section on Neurobiology—
  Phillip G. Nelson, M.D., Ph.D.

Tissue-cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied, using intra-cellular electrophysiologic techniques and correlative light and electron microscopic morphologic methods. Neuron-specific biochemical assays are used to analyze mechanisms of neurodifferentiation. Long-term interactions between nerve and muscle, and the influence of electrical activity on neural development, are of particular interest. Molecular biologic techniques are being used to study gene expression during nervous system development.

- Section on Neuroendocrinology—
  David C. Klein, Ph.D.

Research activities involve environmental, pharmacologic, developmental, and biochemical factors critical to the metabolism and function of the pineal gland. Current studies on this model of neural and neuroendocrine regulation focus on the molecular mechanism involved in the transsynaptic adrenergic cAMP regulation of gene expression. In addition, control of reproductive physiology by the pineal gland is investigated.

Laboratory of Neurochemistry and Neuroimmunology—
Harold Gainer, Ph.D.

This laboratory utilizes the tools of molecular biology and immunology in a cell biological context to study the biosynthesis, packaging, transport, and secretion of biologically neural active peptides and proteins. Various model neuronal systems in organisms ranging from molluscs (squid) to vertebrates (e.g., frog, chick, and rat) are used to examine the development and function of defined neural pathways *in vivo*. Organotypic cultures of these systems are also studied. Techniques which are used include peptide chemistry, monoclonal antibodies and immunochemistry, light and electron microscopy, immunohistochemistry and cytochemistry, subcellular fractionation, and tissue culture.

- Section on Functional Neurochemistry—
  Harold Gainer, Ph.D.

This section focuses on the development and functional organization of peptidergic neurons in the hypothalamus. This includes consideration of the extracellular mechanisms involved in the regulation of specific peptide biosynthesis, as well as secretory vesicle interactions with cytoskeletal proteins during secretion.

Characterizations of specific proteins within these neurons by correlative ultrastructural and immunochemical techniques are made, and the functional roles of these proteins are investigated in both developing and mature neurons. The roles of proteases and membrane proteins involved in neuron:neuron and neuron:glia interactions during development and regeneration are studied.

- Section on Cellular Neurobiology—
  Y. Peng Loh, Ph.D.

This section is concerned with post-translational modifications of proteins and peptides (e.g., limited proteolysis, acetylation, amidation, etc.) in endocrine cells and neurons. Molecular maturation mechanisms are correlated with their intracellular (organelle) locations, and the molecular signals and mechanisms which determine the intracellular routing of specific proteins and peptides are investigated. The effects of intercellular messengers (e.g., neurotransmitters) on the regulation of specific protein and peptide expression are studied. Recombinant DNA techniques are employed to characterize the genes responsible for specific post-translational processing enzymes.

Laboratory of Molecular Genetics—
Igor Dawid, Ph.D.

Investigators in this laboratory use the tools of molecular and cellular biology to answer questions about gene transmission and recombination, and the regulation of genetic functions during development. The range of model systems under investigation includes bacterial and animal viruses, transformed animal cells, yeasts, mouse and *Xenopus* embryos and the fruit fly *Drosophila melanogaster*. Recombinant DNA technology and gene transfer methods are emphasized. The development of novel vectors is being pursued for the introduction and expression of isolated genes in animal cells.

- Section on Developmental Biology—
  Igor Dawid, Ph.D.

Interest is focused on the molecular genetics of development. Gene expression during early embryonic stages of *Xenopus* is studied with the aid of cDNA libraries. Genes preferentially expressed during gastrulation are isolated with the aim of obtaining insight into the molecular events associated with the earliest stages of differentiation. Transposable DNA elements are investigated in *Drosophila* using both classical and molecular genetics. Large regions of the *Drosophila* genome are being isolated using the technique of chromosomal walking so as to analyze the nature of developmental mutations. The organization of ribosomal RNA genes in *Drosophila* is also under study.

- Section on Molecular Regulation—
  Michael Cashel, M.D., Ph.D.

The structure and regulation of activity of genes for ribosomal RNA in *E. coli* are studied using techniques that include *in vitro* mutagenesis and growth rate control by carbon source availability. Determinants for RNA processing and enzymes involved in this process are studied in bacteria and in animals. The functional characteristics of promoter and termination signals in ribosomal genes of *E. coli* are also under study, as is the secondary structure of ribosomal RNA and its role in processing reactions.

- Section on Molecular Structure—
  Jacob Maizel, Ph.D.

This section develops and applies computer and electron microscopic techniques to reveal the information contained in nucleic acid and protein sequences so as to predict their structural and biological properties. Research is undertaken on the synthesis, assembly and structure of nucleic acids, proteins and their combined structures with particular regard to the replication of viruses (adeno-, rhino-, and poliovirus).

- Section on Microbial Genetics—
  Robert Weisberg, Ph.D.

Mechanisms of genetic recombination are studied using bacteriophage lambda. Experiments proceed at the level of genetics, nucleic acid structure, and enzymatic reactions. Studies are conducted to isolate and analyze host factors and the genes that are required for site-specific recombination, and work is carried out to elucidate the molecular mechanisms of the reactions catalyzed by these host factors.

- Section on Animal Viruses—
  Heiner Westphal, M.D.

This section studies the DNA-mediated transfer of isolated genes into mouse eggs, and their integration and expression during subsequent development. This work is being carried out with the aim of studying the regulation of expression of introduced genes in the intact animal. Other work in this section is concerned with the transcriptional regulation of adenovirus. Isolated viral genes and their products are injected into living cells as one aspect of these studies.

Laboratory of Developmental Pharmacology—
Daniel W. Nebert, M.D.

Research in this branch has concentrated on attempts to understand drug-induced gene expression at the molecular level. The laboratory studies mechanisms of drug-induced enzyme regulation, with particular reference to the induction of cytochrome P-450-linked drug metabolizing enzymes by drugs as well as environmental chemicals. There is particular interest in relationships between the genetics of these enzyme systems and mutagenesis, teratogenesis, and carcinogenesis. Other projects within the laboratory employ the classical methods of clinical pharmacology and pharmacogenetics. The long-range goal is to design molecular biology-based assays to predict the individual risk in humans of drug-induced birth defects and chemically induced malignancies.

- Section on Pharmacogenetics and Molecular Teratology—
  Daniel W. Nebert, M.D.

Inbred strains of mice and cells in culture are combined with recombinant DNA and ancillary techniques to study the regulation and gene expression of drug-metabolizing enzymes. Related research projects are in the areas of teratology, and the control of endogenous drug-metabolizing enzymes by hormones and other factors.

- Section on Regulation of Gene Expression—
  Howard J. Eisen, M.D.

This section examines the molecular mechanisms by which steroid hormones, alter gene expression in target cells. Emphasis is on the use of genetic models of hormone- or drug-resistance to study the biochemical functions of receptor proteins and the development of methods for isolation and immunochemical characterization of receptors.

- Section on Drug Biotransformation—
  Ida S. Owens, Ph.D.

Investigations are directed toward Phase II drug metabolism, i.e., conjugation reactions in which enzymes (UDP glucuronosyltransferases) use as substrates bilirubin, endogenous steroids, or oxygenated drugs, carcinogens and other environmental pollutants. Mechanisms of gene expression and enzyme induction are explored via the use of immunochemical and recombinant DNA techniques, inbred strains of mice, and normal and mutant cells in culture. An additional goal is to understand the basis for human genetic diseases involving variants of the Phase II enzymes.

Laboratory of Developmental and Molecular Immunity—
John Robbins, M.D.

- Section on Bacterial Disease Pathogenesis and Immunity—
  John Robbins, M.D.

A primary objective of this group has been to devise methods to increase the immunogenicity of the capsular polysaccharides of *H. influenzae* type b, pneumococci, and *E. coli* associated with invasive human diseases. Semisynthetic conjugates of these polysaccharides have been prepared which convert their immunogenic properties to those of T-cell independence. These conjugates are also used to characterize the ontogeny and genetic control of the serum antibody response in humans. The physical-chemical characteristics of the pertussis toxin, and their relation to this molecule's toxin and protective activities, are also being studied. Monoclonal antibodies to the subunits of the toxin are being used as probes for the cloning of the gene(s) involved in its synthesis.

- Section on Immunoregulation and Cellular Control—
  Edgar Hanna, Ph.D.

Interest is focused on cellular, molecular, and genetic mechanisms involved in regulation of immune systems. Functional regulatory and effector T-cells are established as monoclonal lines. These lines are being phenotyped in order to map pathways of cell circuitry within immune systems.

- Section on Molecular Genetics of Immunity—
  Keiko Ozato, Ph.D.

Modification of transplantation antigen genes at the DNA level is undertaken in order to determine the structural basis for immunological polymorphism and the function of the gene products. Hybrid or mutant mouse H-2 genes are employed in the examination of serological polymorphism and T-cell recognition. Activation of paternal transplantation antigen genes is studied in developing embryos. The phenomenon of immunological unresponsiveness in pregnant females is explored at the level of molecular mechanisms.

Laboratory of Theoretical and Physical Biology—
David Rodbard, M.D.

This laboratory conducts a wide range of multidisciplinary and theoretical studies, applying mathematical, statistical, and computer-based techniques to the analysis of complex clinical, biological, biochemical and pharmacological problems. Experimental work in the laboratory involves the study of ligand binding receptors, as well as electrophoretic, mass spectroscopic, and other biophysical and physical-chemical techniques.

- Section on Theoretical Biology—
  David Rodbard, M.D.

This section is concerned with computerized methods for optimization of experimental design, combined with broadly applicable approaches to data analysis involving mathematical modeling. The enkephalin receptor system is studied as a model for the mathematical analysis of ligand binding. Intensive study is also devoted to the analysis of complex data generated by radioimmunoassays. Problems of cellular structure and morphogenesis are studied using a new image processing system for three dimensional reconstruction. This section is also concerned with the development of new applications of computers in clinical research.

- Section on Macromolecular Analysis—
  Andreas Chrambach, Ph.D.

This section is concerned with the development of quantitative gel electrophoretic methods, both analytical and preparative, and in the application of these methods to the separation and isolation of native macromolecules—especially those relating to immunology and endocrinology. Both the theory of electrophoresis and practical biochemical problems are studied in a long-term effort to develop a versatile, almost universally applicable strategy of macromolecular fractionation.

- Unit on Metabolic Analysis and Mass Spectroscopy—
  Alfred L. Yergey, Ph.D.

This unit develops novel techniques in mass spectrometry and using these methods, undertakes high sensitivity studies of neurotransmitters, steroids, amino acids, and metals such as calcium. Stable (non-radioactive) isotope tracers are employed to investigate the kinetics of metabolism of these molecules in humans, and the time course of serum concentrations of these isotopes is measured by mass spectrometry, employing compartmental analysis.

Pregnancy Research Branch—
Gary D. Hodgen, Ph.D.

The interests of this branch range from fertility regulation and the molecular mechanism of fertilization, through toxicologic aspects of ovarian function, to implantation and the physiology of pregnancy, including the identification of genetic and developmental factors which contribute to fetal, perinatal, and maternal morbidity. These studies employ primates and other animal models as well as laboratory aspects of clinical investigation. Particular emphasis is being given to *in vitro* fertilization using animal models as well as surrogate embryo transfer. Other studies involve the medical and surgical correction *in utero* of fetal metabolic disorders and anomalies, again using primate models.

- Section on Endocrinology—
  Gary D. Hodgen, Ph.D.

This section emphasizes endocrine research in animals, with major emphasis on the endocrine aspects of the reproductive process and related functions of the endocrine system. Basic studies in reproductive biology and fertility are also undertaken, utilizing primates, and topics of interest include the physiology of pubescence, pituitary-gonadal, interrelationships, the induction of ovulation, parturition, and lactation.

- Section on Gamete Physiology—
  Bela J. Gulyas, Ph.D.

This section studies the biochemistry and ultrastructure of gametes. Studies are directed at the regulatory mechanisms of gonocyte development, sperm-egg recognition, aspects of fertilization, and the initiation of embryonic development. Emphasis is also placed on studies of cellular differentiation during early embryogenesis, utilizing micromanipulation technology to introduce a foreign nucleus into enucleated mouse ova.

- Section on Reproductive Toxicology—
  Donald R. Mattison, M.D.

Experiments in this section are concerned with the sites and mechanisms of action of compounds which impair reproductive function; emphasis is on ovarian toxicology. Benzpyrene, an ubiquitous environmental pollutant, is used as a prototype reproductive toxin in animals to explore the mechanism of oocyte destruction. Women treated with cytostatic or cytotoxic drugs are also studied to define the mechanism of ovarian toxicity. Studies on the pharmacology of pregnancy focus on methods of prenatal therapeutics, including the use of fetoscopy, positron emission tomography, and nuclear magnetic resonance imaging.

Endocrinology and Reproduction Research Branch—
Kevin J. Catt, M.D., Ph.D.

Current research is focused on the mechanisms controlling hormone secretion and action, with particular reference to hypothalamic-pituitary hormones and their receptor-mediated responses in endocrine target cells. Studies in progress include the analysis of receptors and actions of hypothalamic peptides (GnRH, somatostatin, CRF, GRF), angiotensin II, ACTH, prolactin, and gonadotropins. The characterization and isolation of peptide hormone receptors, clarification of plasma-membrane related second messenger systems, and the elucidation of the control of steroidogenesis and glycogen synthesis, are major goals of the branch research program.

- Section on Hormonal Regulation—
  Kevin J. Catt, M.D., Ph.D.

Receptor-mediated aspects of peptide hormone action are studied in target tissues regulated by hypothalamic peptides, angiotensin II, and gonadotropins. The mechanisms of peptide hormone action are investigated in isolated pituitary cells (GnRH, CRF, GRF, somatostatin, angiotensin II), adrenal cells (ACTH, angiotensin II), and steroidogenic cells of the testis and ovary (LH, FSH, prolactin, GnRH). In these target cells, the roles of cyclic nucleotides, calcium-dependent processes, and phospholipid turnover, are studied in relation to the control of cellular activity by the regulatory hormones.

- Section on Molecular Endocrinology—
  Maria Dufau, M.D., Ph.D.

This group investigates the molecular basis of peptide hormone action, with particular emphasis on the control of gonadal function; analyzes the nature of gonadotropin receptors and activation of steroid biosynthesis in testis and ovary; and investigates the properties and biological activity of circulating gonadotropins in physiologic regulation and clinical disorders of pituitary and gonadal function.

- Section on Molecular Structure and Protein Chemistry—
  Hao-Chia Chen, Ph.D., Acting

This section is concerned with the development of methods for the elucidation of the primary structure of molecules active in endocrine physiology. Hormones and hormone fragments are isolated and purified and their structure-function relationships established. This section also characterizes and synthesizes macromolecules important to reproductive biology. The structural requirements for agonism or antagonism are determined for various peptide and glycoprotein hormones.

- Section on Adrenal Cell Biology—Charles A. Strott, M.D.

Research is performed on the hormonal and molecular events responsible for adrenal steroid biosynthesis and secretion in mammals, using the comparative approach. Current studies include the identification and purification of specific steroid-binding proteins in the adrenal cortex, the role of the cytoskeleton in steroidogenesis, the detection and characterization of soluble factors in the adrenal that influence the rate-limiting steps of steroid synthesis, and the differential structure and function of the zones within the adrenal cortex.

- Section on Metabolic Regulation—Kuo-Ping Huang, Ph.D.

This group studies the hormonal regulation of glycogen metabolism as a model for determining the complex elements of multiple-site phosphorylation and dephosphorylation in the regulation of rate-limiting enzymes. The section also investigates the mechanisms of action of hormones which affect glycogen metabolism, both in normal tissues and in tissues from diabetic animals.

National Institute of Dental Research

Harold Loe, D.D.S., Dr. Odont.
Director
Marie U. Nylen, D.D.S., Dr. Odont., h.c.,
Director, Intramural Research
Bruce J. Baum, D.M.D., Ph.D.,
Clinical Director

The National Institute of Dental Research recruits about two or three dental and one or two medical staff fellows each year. Initial assignments are for 2 years and may be extended for a third year. Appointments for medical staff fellows usually begin on July 1 and for dental staff fellows on August 1. Selection of candidates is based on program needs and qualifications of candidates. The chiefs of branches and sections screen applications, carry out personal interviews of candidates, and make recommendations to the clinical director, who will make final selection. Selection of candidates for research positions will be made following personal interviews by chiefs of laboratories and branches who have vacancies occurring within their programs. After results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical and basic research program areas and the names of the program chiefs are listed below. A brief sketch of the clinical research areas is provided. Prospective applicants desiring more information should write to Marie U. Nylen, D.D.S., Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, MD 20205.

Dental Staff Fellows

Dental staff fellows spend much of their first year (about two-thirds) providing a wide range of care for patients at the Clinical Center. The remaining time is spent in clinical or laboratory research. The second (and third) year will be spent primarily (about 80 percent) engaged in supervised research with some clinical care responsibilities. Dental staff fellows must have a dental licensure in the United States, a minimum of 1 year hospital dental experience, and a desire for a career in academic dentistry.

Medical Staff Fellows

The medical staff fellow is assigned to one of the clinical research programs within which he or she carries out both clinical and laboratory studies. In addition, the medical staff fellow is responsible for performing medical evaluation and followup of patients accepted under one of the Institute's research protocols. Medical staff fellows may also be assigned to one of the basic research laboratories where they devote all their time to participating in laboratory research. One year of internship and at least 1 year of residency should be completed before the appointment begins.

Clinical Research Branches

Diagnostic Systems Branch—
Richard L. Webber, D.D.S., Ph.D.

Investigations are directed toward research and development of diagnostic techniques. Specific emphasis is placed on radiologic and other noninvasive analysis techniques. The main focus is on interdisciplinary investigations linking clinical expertise with technical competence to facilitate a systems approach to diagnostic problems. Diagnostic systems are designed, modeled, and evaluated with the use of digital simulation techniques. Prototype systems are then developed and tested clinically. Bases for improvement include matching of system elements, image enhancement, and new geometric bases for quantitative analysis of tissue morphology.

Neurobiology and Anesthesiology Branch—

- Clinical Pain Section
  Ronald Dubner, D.D.S., Ph.D., Chief
  Mitchell Max, M.D., Clinical Coordinator

This group conducts research on neural, neuroendocrine, and psychological mechanisms of pain and pain relief in patients with a variety of acute and chronic pain syndromes: post-herpetic neuralgia, diabetic neuropathy, low back pain, myofascial pain-dysfunction, cancer and post-operative pain. Studies are underway to characterize the mechanism of action of opioid peptide release in patients undergoing oral surgery and its correlation with stress and pain; of serotonergic and noradrenergic drugs in patients with post-herpetic neuralgia; of periventricular electrical stimulation in patients with chronic benign pain; and of enkephalin analogues in cancer patients tolerant to morphine. Fellows will acquire experience in the design of analgesic studies, in the use of experimental pain models in humans, in the assessment of pain in humans, in the correlation of pain report and neurochemical mediators in acute and chronic pain conditions, and in clinical pain consultation.

- Neurocytology and Experimental Anatomy Section—
  Stephen Gobel, D.D.S.

This section uses a variety of anatomical approaches to study how noxious inputs, which are transmitted by primary trigeminal neurons, are processed in the central nervous system. Major efforts are directed at the study of the morphology, synaptic connections, and development of second-order interneurons and projection neurons in the medullary (trigeminal nucleus caudalis) and spinal dorsal horns, as well as the identification of the major sources of brainstem descending inputs to these neurons. In addition, a series of experiments are being conducted in which the effects of peripheral nerve transection on synaptic connections are studied.

- Clinical Pain Section—
  Ronald Dubner, D.D.S., Ph.D.

This group conducts research on the assessment of acute and chronic pain and the evaluation of new pain control methods. In psychophysical studies, verbal descriptor scales and metric analog scales are used to measure experimental and clinical pain responses in normal subjects and chronic pain patients. These scales also are employed to assess postsurgical pain and the effects of endogenous pain-suppressing mechanisms. Other studies include the development and application of sedative agents and techniques used in the control of anxiety and apprehension in patients. Research includes physiologic, pharmacologic, and psychological studies of the efficacy and toxicity of combinations of intravenous sedative drugs used in extensive ambulatory surgical procedures.

National Caries Program: Epidemiology and Oral Disease Prevention Program—
James P. Carlos, D.D.S., M.P.H.

- Biometry Section—
  Janet Brunelle, M.S.
- Field Studies Section—
  James P. Carlos, D.D.S., M.P.H., Acting
- Microbial Systematics Section—
  Micah I. Krichevsky, Ph.D.
- Clinical Trials Section—
  Herschel Horowitz, D.D.S., M.P.H.
- Laboratory Methods Section—
  Horace M. Stiles, D.D.S., M.P.H., Ph.D.

This program conducts clinical, field and related studies concerned with the etiology, distribution and prevention of oral diseases. Epidemiologic methodology is employed to investigate such disorders as caries, periodontal diseases and orofacial malformations. Studies utilize broad representative population groups as well as communities with an unusual prevalence of disease conditions. Methods to enhance the effectiveness of fluorides are explored. Clinical trials of caries preventive agents and research into improved methods of analyzing data are conducted.

Clinical Investigation and Patient Care Branch—
Bruce J. Baum, D.M.D., Ph.D.

- Clinical Investigations Section—
  Bruce J. Baum, D.M.D., Ph.D.
- Patient Care Section—
  Michael W. Roberts, D.D.S., M.S.D.

This branch conducts laboratory and clinical studies on normal cellular regulatory mechanisms and alterations occurring in oral disease states. Particular emphasis is placed on exocrine secretion, and white cell functions. Exocrine studies in salivary glands involve hormone/neurotransmitter-receptor interactions, signal transduction events (cyclic nucleotides, Ca^{++}, phospholipids), protein processing and translocation, and water and electrolyte secretion. White cells are studied particularly as involved in periodontal diseases. Cell types studied include neutrophils, lymphocytes, and macrophages. Investigations focus on the regulation of one white cell type by another, and the role of reactive oxygen species in immune responses.

Basic Research Laboratories

Laboratory of Oral Biology and Physiology—
Arthur R. Hand, D.D.S.

- Experimental Morphology Section—
  Arthur R. Hand, D.D.S.
- Enzyme Chemistry Section—
  John E. Folk, Ph.D.

The laboratory conducts basic research on the structure and function of oral tissues, and on the posttranslational modification of proteins. Major emphasis is placed on elucidation of basic mechanisms of cellular secretion. Topics of current studies in this area include the role of the Golgi apparatus in protein transport and packaging; endocytic mechanisms, lysosomal function, and membrane dynamics; structure and function of intercellular junctions; cellular mechanisms regulating gene expression, protein synthesis, and exocytosis; and cell surface receptor localization in salivary glands. Studies of proteins and enzymes are aimed at elucidating their mechanisms of action and biological significance. Particular emphasis is placed on transglutaminases, enzymes which catalyze covalent crosslink formation, and a eukaryotic initiation factor which contains an unusual amino acid formed posttranslationally.

Mineralized Tissue Research Branch—
John D. Termine, Ph.D.

- Bone Cell Biology Section—
  A. H. Reddi, Ph.D.
- Proteoglycan Chemistry Section—
  Vincent C. Hascall, Ph.D.
- Skeletal Biophysics Section—
  Edward D. Eanes, Ph.D.
- Skeletal Matrix Biochemistry Section—
  John D. Termine, Ph.D.

The branch conducts basic research on the physiology, biochemistry, and physical chemistry of skeletal development, regulation, and disorders. Major emphasis is placed on the characterization of mineralized tissue macromolecules including collagens, proteoglycans, and tissue-specific noncollagenous matrix proteins; identification of mechanisms involved in tooth, bone, and cartilage formation; physical and chemical characterization of mineral-forming systems and mineral structure; characterization of the macromolecular organization of skeletal tissue matrices by biophysical techniques; and characterization of the molecular pathology of skeletal tissue diseases. Investigators in the branch use a wide variety of *in vivo*, *in vitro*, and synthetic model systems to explore areas such as the role of bone matrix-derived factors in differentiation of cartilage and bone; macromolecular relationships and matrix-mineral interactions in bone, dentin, and enamel; structure of cartilage proteoglycans and regulation of their biosynthesis and degradation; and ionophore-mediated calcium transport and apatite formation.

Laboratory of Developmental Biology and Anomalies—
George R. Martin, Ph.D.

- Connective Tissue Section—
  George R. Martin, Ph.D.

Research is directed toward the elucidation of teratogen-induced and inherited malformations. Projects include studying molecular mechanisms of cellular development, migration, and tissue formation and interaction. Drugs are used to probe these steps. Alterations in the production of such macromolecules as glycoproteins, collagen, and proteoglycans are also studied. Studies are under way on the regulation of gene activity using recombinant DNA technology. Our emphasis is on normal, mutant, fetal, and malignant cells from bone, cartilage, and other connective tissues. Medical staff fellows in this laboratory are encouraged to pioneer new research areas.

Laboratory of Microbiology and Immunology—
Stephen E. Mergenhagen, Ph.D.

- Microbiology Section—
  Charles L. Wittenberger, Ph.D.
- Cellular Immunology Section—
  Sharon M. Wahl, Ph.D.
- Humoral Immunity Section—
  Ann L. Sandberg, Ph.D.
- Clinical Immunology Section—
  Reuben P. Siraganian, M.D., Ph.D.

Research in microbiology focuses on bacterial ecology and pathogenesis, regulatory mechanisms in the metabolism of carbohydrates by oral bacteria, and on bacterial genetics, with emphasis on plasmid biology. The immunology programs consists of studies on the purification and properties of lymphokines and monokines which are involved in the induction of immunity and inflammation, the regulation of connective tissue metabolism by lymphocytes and macrophages, and the biochemistry of immediate hypersensitivity reactions. While a dental or medical staff fellow is assigned to one of the sections and will work under a senior investigator, considerable opportunity exists for collaboration with scientists in other components of the laboratory.

Laboratory of Oral Medicine—
Abner Louis Notkins, M.D.

The laboratory conducts clinical research on diseases of the oral cavity. The interdisciplinary program emphasizes virology, oncology, and endocrinology. Present research projects focus on the molecular basis for recurrent and persistent viral infections (e.g., herpes simplex), with emphasis on recombinant DNA technology; the etiology and pathogenesis of leukoplakia and papillomas of the oral cavity; virus-induced immunopathology; the application of monoclonal antibody techniques to isolate viral variants; the influence of viral receptors in determining susceptibility to infection; the role of interferon in autoimmune diseases; the etiology of various dermatologic disorders including apthous ulcers; the role of viruses and immunologic factors in diseases of the exocrine glands (e.g., Sjogren's syndrome and salivary gland tumors) and endocrine glands (e.g., diabetes mellitus); and double-blind clinical trials to evaluate the effectiveness of various drugs in the treatment of oral lesions.

Neurobiology and Anesthesiology Branch—
Ronald Dubner, D.D.S., Ph.D.

- Neural Mechanisms Section
  Ronald Dubner, D.D.S., Ph.D.
- Neurocytology and Experimental Anatomy Section
  Stephen Gobel, D.D.S.

Research on peripheral and central nervous system mechanisms of oral-facial sensation is performed by this laboratory. In one major series of studies, behavioral responses in monkeys trained in pain and temperture discrimination tasks are correlated with single-cell neuronal activity recorded in the medullary dorsal horn, thalamus and cerebral cortex. Correlative electrophysiological and morphological studies examine the characteristics of single cells in the dorsal horn and relate their function to morphology and neuronal circuitry. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions.

In other studies, a variety of anatomical approaches are used to study how noxious inputs are processed in the central nervous system. Major efforts are directed at the study of changes in the morphology and synaptic connections of primary afferent neurons and second order neurons in the medullary and spinal dorsal horns following peripheral nerve injury, herpetic lesions and cancer.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D.,
Director

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biologic factors in the environment that can adversely affect man, to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents, and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods, the interaction of multiple agents resulting in enhanced effects, and the modifying effects of variable physical and biologic states within man on the susceptibility to and course of disease induced by these agents.

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, North Carolina. NIEHS is the only one of the 11 Institutes comprising the National Institutes of Health located away from the campus in Bethesda, Maryland.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University of Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, seminars, and other scientific and professional activities associated with the universities.

Medical Staff Fellows

Medical staff fellows work at NIEHS under the direction of Dr. David Rall, Director, and a laboratory or branch chief in the Institute. Each fellow will work directly under a senior scientist in an area of research chosen by the fellow and the Institute. The initial appointment is for 2 years. These appointments are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. NIEHS does not have clinical facilities; however, medical staff fellows may work out informal arrangements with the clinical staff at the University of North Carolina and/or Duke University Medical School. Prospective applicants desiring more information should write to the Scientific Director, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

Intramural Research Laboratories

Laboratory of Pharmacology—
John R. Bend, Ph.D.

The toxic effects of low-level and/or chronic exposure to environmental constituents or contaminants on mammals and marine species are studied in this laboratory. Interactions (on or within the animal) of these environmental factors with each other and with drugs are also studied. Projects currently under way include: toxication-detoxication systems in the liver, lung, and skin and effects of pollutants on these systems and the balance between toxication and detoxication reactions; age-related changes in toxication-detoxication systems in various organs; uptake, storage, metabolism, and release of chemicals in the lung and liver; species differences in xenobiotic disposition and metabolism; and studies on the formation and metabolism of reactive metabolites of hydrocarbons in various marine species and purification and comparison of components of toxication-detoxication systems in various organs.

Laboratory of Reproductive and Developmental Toxicology—
John A. McLachlan, Ph.D.

Scientific efforts are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis with *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratology potential; study the molecular mechanisms underlying cellular differentiation; evaluate perinatal aspects of enzymology, endocrinology, and pharmacokinetics with regard to environmental toxicity; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects that do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of toxicity with the use of *in vitro* cells and tissues, lower animals, and biochemical test systems.

Laboratory of Behavioral and Neurological Toxicology—
Clifford L. Mitchell, Ph.D.

Research is concerned with the study of changes in behavior and neurologic function produced by long-term exposure to low levels of many chemical and physical agents present in the environment. Special consideration is being given to the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurologic abnormalities, studies concerning the mechanisms whereby environmental factors produce behavioral and neurotoxic effects, and studies concerning the conditions that predispose individuals to the behavioral and neurotoxic effects of environmental factors.

Laboratory of Pulmonary Function and Toxicology—
Paul Nettesheim, M.D.

The long-range objectives of this laboratory are to obtain through animal studies information needed to provide the scientific basis for the prevention of respiratory diseases which might have an environmental etiology. The intramural program is studying mechanisms of pulmonary biology and pathology in appropriate experimental models. Research is being pursued in pulmonary endocrinology, prostaglandins, biochemical pathology, environmental carcinogenesis, pulmonary cell biology, and pulmonary pathology.

Laboratory of Molecular Biophysics—
Colin F. Chignell, Ph.D.

This branch supports research programs and collaborates with Institute laboratories on studies on the chemistry of suspect environmental agents. The branch utilizes, develops, and improves analytical methodology for specified agents which includes immunoassay and instrumental methods such as mass and magnetic resonance spectrometric techniques and high-pressure liquid chromatography. Suspect environmental agents and their conversion products are synthesized and characterized. Research studies on environmental agents, biological materials, and their metabolites emphasize biomechanism elucidation.

Laboratory of Genetics—
Burke Judd, Ph.D.

This laboratory concentrates on studies on the genetic structure of populations and on the structural and functional organization of higher eukaryotic genes, using model systems such as *Drosophila* and cultured mammalian cells. A group in genetic enzymology seeks to develop rapid and efficient methods for the purification of specific macromolecules, proteins, and nucleic acids. One project in chemical genetics focuses on the analysis of mutant mammalian proteins and DNA using primary sequence analysis.

Biometry and Risk Assessment Program—
David G. Hoel, Ph.D.

The Biometry and Risk Assessment Program conducts basic and applied environmental health-oriented research in the areas of risk assessment, statistics, biomathematics, and epidemiology. In addition it assumes responsibility for data management and statistical analysis in the Toxicology Research and Testing Program, and provides statistical, mathematical, data processing, and computer engineering support to the other programs of the Institute. Organizationally, the program is divided into a Statistics and Biomathematics Branch, an Epidemiology Branch, and a Computer Technology Branch.

Statistics and Biomathematics Branch—

The Statistics and Biomathematics Branch conducts a broad research effort ranging from statistical analysis to biomathematical modeling aimed at developing new or improved methods for quantitative risk estimation, particularly in the areas of carcinogenesis, mutagenesis, and reproduction. Branch scientists also maintain an active research program in statistical methodology relevant to design and analysis issues arising in laboratory experimentation with special emphasis on toxicological screening assays.

Epidemiology Branch—

The Epidemiology Branch initiates field studies of human disease, particularly chronic disease, due to environmental pollutants. The branch also investigates the effects of environmental toxins on fetal and child development and conducts basic and applied research in laboratory support methodology involved in the monitoring of human populations.

Computer Technology Branch—
Thomas A. Clemmer, M.S.

The Computer Technology Branch operates the Institute's computer systems and provides programming consultation services, including software systems development, to Institute personnel. It also maintains an active computer engineering group and furnishes systems analysis and project management support to various groups throughout the Institute.

Toxicology Research and Testing Program—
Ernest E. McConnell, D.V.M.
Acting

The Toxicology Research and Testing Program—the NIH operating component of the National Toxicology Program—develops, validates, and evaluates methods for toxicity testing of chemicals and other environmental agents; is responsible for toxicity testing, using both short- and long-term bioassays, to determine or ascertain toxicity of chemicals and other environmental agents; coordinates and communicates test development and testing program with other government agencies; and disseminates results of research, testing, methods development, and validation efforts to the scientific and public communities and to the regulatory agencies.

National Institute of General Medical Sciences

Ruth L. Kirschstein, M.D.,
Director
Sara A. Gardner, Ph.D.,
Director, Pharmacology
Research Associate Program

Pharmacology Research Associates

The National Institute of General Medical Sciences (NIGMS) has 11 positions (medical staff fellow and staff fellow) available each year for pharmacology research training. The Pharmacology Research Associate Program seeks to develop leaders in pharmacologic research for key positions in academic, industrial, and Federal research laboratories. It is intended for those who have made a commitment to pharmacology in their training or research, and for those with backgrounds in clinical medicine or basic science who wish to acquire specialized experience in the field of pharmacology.

Those who are appointed begin on July 1 and receive 2 years of postdoctoral training in one of the participating laboratories of the National Institutes of Health (NIH) and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). Fellows engage in research relating the principles of pharmacological sciences to contemporary biomedical problems. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, biophysics, and instrumentation is also available. During their tenure, pharmacology research fellows devote the major portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities. A variety of laboratory problems and different research approaches advance both the work in progress and the competence of the prospective independent investigator.

Professional growth is stimulated through personal guidance by outstanding senior NIH and ADAMHA scientists who serve as preceptors. Preceptors and research fellows are matched by a mutual selection process after personal interviews.

Candidates for pharmacology research associate positions include those who will have received either the Ph.D., M.D., or equivalent degree and have research experience or training in areas relevant to pharmacology. Those with research experience in a related area who wish to further their development in pharmacology are also eligible. Applicants with the M.D. degree may use this opportunity to further their training in basic pharmacologic research in preparation for a career in clinical pharmacology or a related discipline.

Program Areas

The choice of a specific laboratory depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may, with the approval of the Pharmacology Research Associate Advisory Committee, request any senior NIH or ADAMHA scientist as a preceptor. Since the objective of this program is to offer post-doctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities.

Clinical Pharmacology

An opportunity is available for 2 years of research training specifically in the area of clinical pharmacology. Applicants for research training in clinical pharmacology should have the M.D. degree and a minimum of 1 year, preferably 2, of graduate medical training (internship, residency), as well as a demonstrated interest in clinical pharmacology. The program emphasizes laboratory methods applicable to pharmacological research in man but also includes training in such general clinical pharmacological principles as pharmacokinetics, pharmacodynamics, biostatistics, and drug evaluation.

Preceptors for the clinical pharmacology fellows are investigators who are actively engaged in clinical pharmacological research in the Warren Grant Magnuson Clinical Center, NIH. These preceptors will include but are not limited to:

Bruce A. Chabner, M.D., Director, Division of Cancer Treatment, National Cancer Institute
James R. Gillette, Ph.D., Chief, Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute
Harry Keiser, M.D., Clinical Director, National Heart, Lung, and Blood Institute
Charles Myers, M.D., Chief, Clinical Pharmacology Branch, National Cancer Institute
Daniel W. Nebert, M.D., Chief, Laboratory of Development Pharmacology, National Institute of Child Health and Human Development
Snorri S. Thorgeirsson, M.D., Ph.D., Acting Chief, Laboratory of Carcinogen Metabolism, National Cancer Institute

William Z. Potter, M.D., Ph.D., intramural clinical pharmacologist, serves as coordinator of each fellow's overall training in clinical pharmacology. The clinical pharmacology fellows' research experiences are planned individually to meet the needs dictated by previous training, experience, and career goals. This research experience will involve both laboratory and human investigation.

A training plan, including formal coursework, is developed for each fellow. A series of seminars are organized with the participation of the clinical pharmacology fellows to ensure that their needs are met. The fellows also help develop and instruct in the medical student elective program in clinical pharmacology.

In addition to a primary involvement in clinical pharmacological research, the fellows participate in clinical pharmacology rounds. These rounds are directed on an alternating basis by preceptors from the different categorical areas to ensure broad exposure to a wide range of problems in clinical pharmacology. Part of the clinical pharmacology experience involves collaborating with the coordinator in clinical pharmacology consultations at the Clinical Center.

An applicant may be considered for both the regular pharmacology research fellowship program and the clinical pharmacology option. Further information may be obtained from the Pharmacology Research Associate Program, NIGMS, NIH, Westwood Building, Room 919, Bethesda, Maryland 20205, (301/496-7707).

National Cancer Institute

Laboratory of Carcinogen Metabolism—
Snorri S. Thorgeirsson, M.D., Ph.D.

This laboratory conducts investigations on: malignant transformation in human and animal cells by chemical carcinogens and other cancer-causing agents; the mechanism of the regulation of gene expression by hormones and growth factors; the cellular events which mediate the conversion of normal cells into neoplastic cells; and the chemical structure and conformational aspects of relevant biopolymers, chemical carcinogens, and carcinogen-biopolymer adducts using rigorous spectral and chemical methods.

Clinical Pharmacology Branch—
Bruce A. Chabner, M.D.
Charles Myers, M.D.

Dr. Chabner's laboratory is concerned with the mechanism of action and pharmacokinetics of, as well as mechanisms of resistance to, the antimetabolite classes of antineoplastic drugs. Its primary interest at present is the process of metabolic conversion of antifolic compounds to polyglutamate metabolites. This conversion produces an intracellular metabolite which has different pharmacokinetic and biochemical properties than the parent compound and which appears to extend the duration of action of the drug. The laboratory has also been concerned with the clinical pharmacology of methotrexate, specifically with the use of test doses to predict drug clearance and to modify the doses in patients who receive high-risk forms of methotrexate therapy. Other projects which the laboratory has recently completed include studies of the genetic and biochemical basis of antifolate resistance in cloned human tumor cells, determinations of cytotoxicity for the cytidine class of antimetabolites (cytosine arabinoside), and the mode of action of fluoropyrimidines. Collaborations are ongoing to study the role of the pineal hormone, melatonin, in determining the risk of development of breast cancer in experimental models.

Dr. Myers' laboratory is involved in the biochemistry of adriamycin-iron complexes, including their free radical products. This process involves examination of how these complexes bind to and cleave DNA. In addition, studies are planned to assess the biologic role of these drug-metal complexes. The other major area in Dr. Myers' laboratory revolves around the enzymatic defenses of mammalian cells against free radical attack. In the process, the investigators appear to have discovered a new family of peroxidases which they are in the process of purifying and characterizing. Projects are available investigating the role of these enzymes in the detoxification of drug-induced free radicals.

Laboratory of Experimental Therapeutics and Metabolism—
Michael R. Boyd, M.D., Ph.D.

The research programs of this laboratory are interdisciplinary in nature and fall into two major areas. One area is analytical and clinical pharmacology involving studies on qualitative and quantitative aspects of the metabolism and disposition of cancer chemotherapeutic agents using experimental systems, as well as in a clinical setting. Problems are selected for their relevance to the development and/or evaluation of new chemotherapy protocols, and frequently are pursued in collaboration with other NCI laboratories. The other major research area concerns the elucidation of fundamental chemicobiologic interactions underlying chemical-induced cytotoxicity and carcinogenicity to specific target organs and target cells. Of particular interest is the role that the drug-metabolizing enzymes play in the pathogenesis of extrahepatic target tissue toxicities, especially those involving the lungs or the kidneys. Investigations of hepatic and extrahepatic metabolic "activation" and "deactivation" systems are of interest, as are investigations of the biochemical, physiologic, and morphologic consequences of the *in situ* generation of alkylating metabolites in both normal and neoplastic extrahepatic target cells. These studies are intended not only to characterize mechanisms of chemical-induced cancer or cell necrosis, but also to provide a basis for the design of new anticancer drugs with optimal tumoricidal activity but minimal toxicity to normal tissues.

Laboratory of Medicinal Chemistry and Pharmacology—
David G. Johns, M.D., Ph.D.

This laboratory conducts an integrated program for the rational development of antitumor agents, carries out the synthesis of compounds with potential antitumor activity, and assesses the effects of such agents on experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites—nucleic acids, cell membranes, and microtubular protein and enzyme systems. Of special concern are agents that act as "stoichiometric" or "titrating" enzyme inhibitors, with current emphasis on the interaction of 2′-deoxycoformycin with adenosine deaminase and on the biochemical and pharmacologic effects of 2′-deoxycoformycin when used in combination with adenosine analogs. Another area of current interest is the maytansine group of mitotic inhibitors and the nature of their binding with microtubular protein.

- Drug Metabolism Section—
  Richard L. Cysyk, Ph.D.

This section is involved in studies of the metabolism, mechanism of action, and mechanism(s) of selective toxicity of antitumor agents. New drugs are designed, synthesized, and evaluated for their effects on biochemical pathways critical to cell survival. Drugs are tested for cytotoxicity using *in vitro* cell cloning techniques and for antitumor activity in animals with tumors. An emphasis is placed on identifying endogenous factors that alter drug toxicity and that influence differential drug toxicity. One area of current interest is the development of analytical methods using stable labeled compounds in combination with mass spectrometric techniques to study the flux through the *de novo* pyrimidine pathway *in vivo.* A goal of this research is to understand the regulation of *de novo* nucleoside synthesis in organs and tumors *in vivo.*

- Applied Pharmacology Section—
  Robert I. Glazer, Ph.D.

This section conducts molecular studies of the mechanism of action of anticancer drugs in human tumor cell lines in tissue culture. Areas currently receiving the greatest emphasis include the synthesis and processing of ribosomal RNA, the transcription of specific messenger RNAs by *in vitro* hybridization with cloned DNA probes, and polyamine- and calcium-phospholipid-dependent protein phosphorylation. The classes of drugs under investigation include adenosine and pyrimidine analogs, human immune interferon, and synthetic 2′, 5′-oligoadenylate analogs. The primary purpose of these studies is to relate the cytotoxicity of these anticancer agents, as assessed by clonogenic assay, with their mechanism of action at the molecular level. A variety of the latest molecular biological techniques are employed in investigating the various facets of this problem.

- Biochemical Toxicology Section—
  Theodore E. Gram, Ph.D.

Research interests include the chemical and biochemical mechanisms involved in interactions between xenobiotics and biologic materials that result in toxic responses; studies of the morphologic reaction to toxic response to determine if the morphologic alterations precede, coincide with, or follow toxicity; investigations to determine whether toxicity is spontaneously reversible and what factors, if any, augment or diminish the toxicity; and studies on whether toxicity exhibits organ specificity and, if so, how it might be explained. The section is particularly interested in the role of drug oxidation and conjugation in the detoxification and toxication of xenobiotics. Past work has been oriented toward the function of microsomal and cytosol enzymes of the liver, lung, and kidney in these phenomena. Lung studies lung have been conducted in intact animals, the isolated perfused lung, slices from normal lung and lung tumors, tissue homogenates, and subcellular fractions. This group is also interested in the functions that tissue uptake, binding, metabolism, and clearance have in drug-related specific end-organ toxicity. Investigations are currently in progress to evaluate these questions since they relate to the serious and dose-limiting problems of pulmonary fibrosis associated with a number of oncolytic agents such as bleomycin, renal necrosis resulting from platinum compounds, and myocardial fibrosis associated with adriamycin.

- Molecular Biology and Methods Development Section
  Marco Rabinovitz, Ph.D.

Attention is focused on the development of approaches for the potentiation of cancer chemotherapeutic activities. Nutritional and pharmacologic regimens are first explored in tissue culture and then extended to the tumor-bearing animal in attempts to direct cytotoxic agents toward the tumor cell and away from sensitive normal tissues. New cytotoxic and potentiating agents are also synthesized to achieve this goal. Biochemical studies include the analysis of inhibition kinetics of binding, transport, and detoxication of cytotoxic agents in sensitive and resistant tumor cells and in sensitive host tissues. An investigator is encouraged to use several of the above methodologies in pursuit of the solution to a particular problem.

- Laboratory of Medicinal Chemistry and Pharmacology Pharmacokinetics and Pharmacodynamics Section—
  Daniel S. Zaharko, Ph.D.

This section is involved with pharmacologic investigations of cancer chemotherapeutic agents. Research efforts are currently directed toward studying the relationships between *in vitro* and *in vivo* pharmacological parameters of drugs, such as exposure time and threshold concentrations. Modulation of drug effects with biochemical intermediates and other drugs is also of interest. Most studies utilize rodent species and involve pharmacokinetics, radioactive tracers, chromatography (HPLC) and *in vitro* techniques of cell growth and soft agar cloning.

The research interests of this section are the relationship between pharmacokinetics and drug effects, the biochemical selectivity of anticancer agents in different organs and tissues, and the transport and role of nucleosides in the biochemical balance of the whole animal.

National Heart, Lung, and Blood Institute

Laboratory of Chemistry

- Section on Physiological Chemistry—
  John J. Pisano, Ph.D.

Normal and pathologic states in humans are studied at the molecular level. Under investigation are neuroactive (enkephalins) and vasoactive peptides (bradykinin and angiotensin), precursor proteins of the peptides (kininogens), and the enzymes (kallikreins) involved in the biosynthesis and degradation of peptides. Modern anayltic techniques such as gas chromatography, high-pressure liquid chromatography, affinity chromatography, mass spectrometry, and radioimmunoassay are commonly employed. Research is currently directed toward the discovery of naturally occurring biologically active peptides, the study of hypertension, new factors regulating coagulation and fibrinolysis, and micromethods for the detection and amino acid sequence analysis of polypeptides.

Laboratory of Chemical Pharmacology— James R. Gillette, Ph.D.

- Section on Drug-Enzyme Interaction— James R. Gillette, Ph.D.

Various aspects of drug disposition are investigated, including the relationship between drug metabolism and drug toxicity. The main objective of this section has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolities. The section also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal levels.

- Section on Cellular Pharmacology— Michael A. Beaven, Ph.D.

This section has an interest in the study of drug action at the cellular level. Current work includes: studies on the mechanism of repression of lymphocyte blast tyransformation by anti-inflammatory drugs; the inhibition of white cell recruitment and chemotaxis in inflammatory reactions by anti-inflammatory drugs; research on the release and metabolism of histamine and other active factors during inflammatory and allergic reactions; and studies with purified populations of cells from the gastric mucosa and capillary endothelial cells to determine distribution of histamine receptors and biochemical responses to histamine and other active hormones.

- Section on Pharmacological Chemistry—Lance R. Pohl, Pharm.D., Ph.D.

This section studies the mechanisms of metabolism, action, and toxicity of pharmacologically active chemicals. It includes studies of the identification of active substances formed in the body, the biochemical basis of their pharmacolgic and toxicologic actions, and the characterization and regulation of the enzymes that either produce or metabolize these agents. This section is particularly interested in the mechanism of drug-induced autoimmune diseases. In addition, it is involved in the study of the mechanism and regulation of the turnover of cytochromes P-450 in the liver, adrenals, testes, and ovaries.

Hypertension-Endocrine Branch—

- Section on Biochemical Pharmacology— Walter Lovenberg, Ph.D.

Research is directed toward understanding the regulation of monoaminergic systems and the relationship of these systems to specific diseases. Both biochemical and pharmacologic approaches are used to investigate various neuronal systems and how information is transmitted between cells. This group is particularly interested in the role of cyclic nucleotides and calcium in these receptor-mediated responses. Some of the current research projects are: molecular characterization of the monoamine biosynthetic enzymes; regulation of catecholamine and serotonin synthesis by protein phosphorylation reactions; molecular events involved in the transduction of nerve impulses into changes in target cell proteins and enzyme levels in small blood vessels and the pineal gland; the distribution and physiologic role of the hydroxylase cofactor (tetrahydro-biopterin); the role of calmodulin in regulation of the activity of neuronal systems; the biochemical mechanism of antihypertensive and antipsychotic drugs; and the role of the central and peripheral nervous systems in the regulation of blood pressure in experimental animals and man. The work encompasses several fields, including pharmacology, enzymology, protein chemistry, and molecular biology.

- Section on Biochemical Pharmacology— Ingeborg Hanbauer, Ph.D.

Work in this laboratory focuses on regulation of the release of enkephaline-like peptides from adrenal glands. The effects of electrical stimulation of the splanchnic nerve, and those of specific agonists and antagonists of nicotinic or opiate receptors, on the release of met-enkephaline-like peptides are investigated. The peptides released from the adrenal chromaffin cells into the adrenal venous blood are characterized by HPLC and RIA using specific antibodies.

Work is also focused on pharmacologic and biochemical aspects of the regulation of striatal dopamine receptors. The regulation of adenylate cyclase-linked dopamine receptors is studied in the corpus striatum, with particular attention on two of its functional states, sub- and supersensitivity. These studies comprise measurements of dopamine recognition sites, G/F protein, adenylate cyclase clamodulin, and phosphorylation and dephosphorylation of membrane proteins and protein kinases.

Laboratory of Biochemical Genetics—
Marshall W. Nirenberg, Ph.D.

- Section on Molecular Biology—
  Marshall W. Nirenberg, Ph.D.

This section studies basic problems in molecular biology and biochemistry, particularly those that pertain to the development of the nervous system. Current research is focused on elucidating mechanisms that regulate gene expression using recombinant DNA techniques. Many monoclonal antibodies have been generated and are being used as probes for synaptic and other antigens. Cultured cells are used in many studies. Research is also being conducted on cyclic nucleotides, receptors, ion channels, and cell recognition.

Research is also directed toward the mechanism of action of opiate peptides, dependence on and tolerance to these compounds, and the role of opiate receptors in the regulation of adenylate cyclase activity.

- Section on Macromolecules—
  Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms. One area of interest involves a study of the hypothalamic tripeptide, and thyrotropin-releasing factor. The biochemical and pharmacologic properties of a newly discovered metabolite of thyrotropin-releasing factor are under investigation. These experiments may lead to a better definition of the metabolism and mechanism of action of this hormone. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells. Current information suggests that cyclic AMP concentrations in *Escherichia coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells.

Laboratory of Cellular Metabolism—
Martha Vaughan, M.D.

This laboratory conducts research directed toward understanding the regulation of cyclic nucleotide synthesis and degradation. Cyclic AMP synthesis by the membrane-associated adenylate cyclase complex is controlled by stimulatory and inhibitory agonists such as hormones and drugs acting through cell-surface receptors. The signal generated by receptor-agonist interaction is transmitted to the cyclase catalytic unit via GTP-dependent coupling proteins, which are also the targets for covalent modification (ADP ribosylation) catalyzed by bacterial toxins (*e.g.,* cholera toxin, pertussis toxin) that activate the cyclase. Areas of current study include: (1) cell biology: the effects of hormones and toxins on cyclic nucleotide content and the formation of arachidonate metabolites (*i.e.,* prostaglandins leukotrienes) by cultured cells; (2) membrane biochemistry: the molecular mechanisms of the interaction of adenylate cyclase components (analyzed, in part, with site-specific monoclonal antibodies); the kinetics of receptor-ligand interaction, and the effects of toxin-catalyzed ADP ribosylation on the interaction of coupling proteins with receptors and the catalytic unit; (3) enzymology: the identification of ADP ribosyltransferases and their substrates in animal cells, the effects of ADP ribosylation on enzyme function, the regulatory properties of the phosphodiesterases that degrade cyclic nucleotides, and the mechanisms by which calmodulin modifies the activities of phosphodiesterase and other proteins with which it interacts; and (4) molecular biology: the regulation of gene expression for components of the adenylate cyclase system and the effects of translational control on the production of cyclase components.

National Institute on Alcohol Abuse and Alcoholism

Clinical Intramural Research Program
Markku Linnoila, M.D., Ph.D.

The laboratory consists of a 10-bed research ward, 11 modules of laboratory space, and an animal facility in Building 10. There are five sections and two units in the laboratory. The major research interests consist of treatment and prevention of alcoholism and alcohol withdrawal. New medications with specific mechanisms of action will be tried in detoxication and maintenance treatments of alcoholics. Both the pharmacokinetics and pharmacodynamics of the drugs are carefully monitored 24 hours a day with EEG, ECG, and BP telemetry as well as temperature and activity measurements. Cerebrospinal fluid, plasma and urine monoamines, and prostaglandins are quantified with mass fragmentography and liquid chromatography. Peptide neuromodulators are measured with radioimmunoassays after separation with chromatography. Receptor functions are measured in blood cells and in animal experiments. Brain functioning is measured with electrophysiological and imaging techniques over and beyond behavioral observations. Liver functioning will be characterized using C_{13}-labeled drugs as tools to evaluate metabolic rates of both flow- and enzyme-dependent drugs. Preclinical tests of drugs having potential for treatment of alcoholism will be conducted in the Neuroscience Section of the laboratory. The Unit of Genetic Studies will use two-dimensional protein electrophoresis to detect polymorphisms in families with alcoholics and subsequently will engage in chromosomal mapping.

Laboratory of Preclinical Studies—
Forrest F. Weight, M.D.

Research investigations in this laboratory center on the physiology and pharmacology of neurons and synapses in the central and peripheral nervous system. The general areas studied include: regulation of nerve cell excitability and neurotransmitter release, cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin, and GABA; membrane mechanisms of neurotransmitter and drug actions; cellular actions of peptides such as enkephalins, endorphins, and LH-RF; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbiturates, opiates, and other neuroactive substances. The research techniques available to a medical staff fellow include: extracellular unit recording and iontophoresis of drugs and putative transmitters to single neurons in the CNS; intracellular recording and intracellular injection techniques; use of *in vitro* preparations, such as CNS slices, sympathetic ganglia, and tissue culture for studying the pharmacology of drug-receptor interactions; voltage and patch clamp techniques for studying the ionic basis of membrane permeability changes involved in drug and transmitter actions.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

Arthritis and Rheumatism Branch—

- Section on Chemical Immunology—
  Henry Metzger, M.D.

This section is studying mast cell secretion mediated by the high-affinity receptor for immunoglobulin E. The studies involve isolation, characterization, and reconstitution (into liposomes) of the receptor and exploration of biochemical perturbations during triggering. This system serves as a powerful model for examining at a molecular level the proximal events in cellular secretion mediated by a cell-surface receptor.

- Section on Pharmacodynamics—
  John W. Daly, Ph.D.

This section is engaged in research on the formation, degradation, and role of cyclic nucleotides in the nervous system, including: the mechanisms of action of forskolin on adenylate cyclase; development of selective agonists/antagonists for receptors for catecholamines, adenosine, and other neuroregulators; the relationship between membrane potential, phospholipid turnover, and generation of cyclic nucleotides; the interrelationship of adenosine and calcium in the regulation of cyclic nucleotide formation and action; and morphologic entities (neurosomes/gliosomes) associated with cyclic nucleotide formation and action. It also conducts research on the effect of drugs on neuronal and muscular function, in particular the transport and function of ions such as sodium, potassium, and calcium, using radioactive alkaloids such as batrachotoxin, histrionicotoxin and pumiliotoxin to investigate sites associated with transport of such ions.

- Section on Pharmacodynamics—
  Phil Skolnick, Ph.D.

The research program is concerned with understanding the relationship between receptors for psychoactive compounds and the endogenous substances which normally interact with these receptors. The techniques employed in studying these relationships range from biochemical investigations of the nature of endogenous ligands and their interaction with membrane receptors to the use of both primary and transformed cell culture models and classical "whole animal" pharmacology. Specific projects currently under investigation include: (1) differential regulation of CNS benzodiazepine receptors by pharmacologically defined "agonists" and "antagonists;" (2) study of the role of ionophores (*e.g.*, calcium and chloride ions) in neuronal excitability; and (3) the physiologic and pharmacologic modulation of recognition sites and uptake systems in the CNS for psychoactive drugs (*e.g.*, phenethylamines such as amphetamine) and the relationship of such sites to their functional roles).

- Section on Oxidation Mechanisms—
  Donald M. Jerina, Ph.D.

The primary interest of this section is the elucidation of the fundamental mechanisms by which drugs and environmental chemicals are transformed in the body. In many instances oxidative metabolism produces chemically reactive metabolites which are responsible for the cytotoxic, mutagenic, and carcinogenic activity of the drug substrate. Recent studies have been concerned with the roles of the cytochrome P-450 system and epoxide hydrolase in the formation of mutagenic and carcinogenic metabolites from the polycyclic aromatic hydrocarbons. Emphasis is on modern instrument techniques such as high pressure liquid chromatography, high resolution mass spectrometry-gas chromatography, and high-resolution magnetic resonance in the study of metabolism catalyzed by homogeneous cytochromes P-450, epoxide hydrolase, and the glutathione transferases.

Laboratory of Biochemical Pharmacology—
Herbert Tabor, M.D.

Work in this laboratory is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (*e.g.*, spermidine and spermine) and amino acids. The polyamines occur in large amounts in biologic materials and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Current work is directed toward the mechanism and *in vivo* significance of these effects. These studies provide experience with a variety of techniques (enzyme characterization, bacteriophage methodology, nucleic acid chemistry, and isotopic and nonisotopic synthesis). Special emphasis is placed on the use of plasmids and techniques involving DNA cloning, as well as on various genetic techniques in both *Escherichia coli* and yeast.

Other work includes studies on control mechanisms for other enzymes in bacteria and mammalian cell cultures, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability. Investigations are also carried out on developmental biology and organ regeneration in the rat and aim at identifying state of cell differentiation. Other studies involve the biology and immunology of the complex carbohydrates of animal cell surfaces.

- Section on the Genetics of Simple Eukaryotes—
  Reed B. Wickner, M.D.

This section is studying the genetic control of replication of a set of double-stranded RNAs found in virus-like particles in the simple eukaryote *Saccharomyces cervisiae* (yeast). These double-stranded RNAs determine the "killer trait," the production of a toxin lethal to yeast not carrying the virus. The laboratory has found that replication of the double-stranded RNA genome involves a large number of chromosomal genes, several genes on the double-stranded RNA segments themselves, and a mitochondrial gene. These components show many complex functional interactions. Current work to examine the nature of these genes and the mechanisms of their interactions involves genetics, enzymology, pharmacology, molecular cloning, and molecular biology.

Laboratory of Chemistry—Microanalytical Services and Instrumentation Section—

S. Stoney Simons, Jr., Ph.D.

The objective of this group is to define, on a molecular level, the biological properties of the receptors for steroid hormones. Major efforts are devoted to studying the activities of glucocorticoid receptor-steroid complexes prior to their effects on gene transcription. Current investigations concern the biochemistry of covalent, affinity-labeled glucocorticoid receptor-steroid complexes, purification of the covalently labeled complexes, a comparison of agonist versus antagonist action among various steroid hormones, and spectrofluorometric studies of steroid-receptor interactions. The experimental approaches include tissue culture, synthetic organic chemistry, whole-cell bioassays, cell-free biochemical studies, gel electrophoresis, binding to cloned DNA sequences, protein and DNA analysis, and fluorescence spectroscopy.

Laboratory of Biochemistry and Metabolism—

William B. Jakoby, Ph.D.

This group approaches the problems of detoxication at the level of purified enzymes. Proteins are brought to the stage of homogeneity and are studied with respect to catalytic, binding, and regulatory properties. Emphasis is on the mechanism of action of those enzymes catalyzing conjugation reactions with glutathione or adding sulfate or methyl groups. Currently, a natural inhibitor of methylation is being evaluated at both enzyme and cell culture level.

Laboratory of Cell Biology and Genetics

- Section on Cell Biology and Bichemistry—
  Harvey B. Pollard, M.D., Ph.D.

The primary interest of this group is in mechanisms of secretion of proteins, hormones, peptides, and transmitters from neuroendocrine and other cells. The systems it is particularly interested in include chromaffin cells, islets of Langerhans, platelets, and synaptosomes. Critical problems now under investigation include how secretory vesicle assembly is regulated, how cytoskeletal proteins interact with subcellular organelles, how calcium acts to fuse secretory vesicles to plasma membrane, and how the subsequent release of vesicle contents during exocytosis occurs. The approach of this laboratory is to search for special proteins that could mediate such events. Techniques used include biochemistry, light and electron microscopy, electrophysiology, and cell culture.

Laboratory of Cell Biology and Genetics

- Section on Membrane Biology—
  Loretta Leive, Ph.D.

This laboratory studies how structure is related to function in biological membranes. One major area of interest is phagocytosis in macrophages, which is being approached in two different ways. First, mutants in general phagocytosis have been selected from a permanently differentiated macrophage cell line, and the biochemical changes responsible for these defects are being explored. Second, a less-differentiated macrophage cell line which cannot carry out receptor-mediated phagocytosis was found to be induced to do so by dimethyl sulfoxide; several other cell functions were unaffected. The physiological and biochemical changes occurring during this induction are being studied.

Another major area of interest is the influence of bacterial membrane components on mammalian defense mechanisms. The laboratory is examining the influence of the polysaccharide component of bacterial lipopolysaccharide on complement activation. It has been found that changes in a single sugar residue can affect the rate of complement activation via an alternative pathway, and the laboratory is now investigating the molecular mechanism responsible for this alteration. Also being studied is the influence of bacterial membrane proteins and polysaccharides on phagocytosis and on antibody- or complement-mediated killing. Other projects related to these areas of interest will be added as appropriate.

Diabetes Branch—
Jesse Roth, M.D.

The Diabetes Branch studies receptors for peptide hormones, especially insulin, insulin-like growth factors, and growth hormone. Current projects are focused on the role of receptors and receptor antibodies in disease states, genetic disorders of the insulin receptor, biosynthesis of receptor components, the role of receptors in hormone action at the target cell, morphologic correlates of hormone binding to receptor (electron microscopy and immunocytochemistry), and receptors on circulating cells and cells in tissue culture. Other projects examine insulin and insulin receptors in the central nervous system; the evolutionary origin of insulin, ACTH, somatostatin, and other peptide messenger molecules; and the role of such molecules in primitive (unicellular) organisms. The clinical service of the Diabetes Branch provides continuous access to patients with disorders of glucose metabolism and receptor-related disorders.

National Institute of Child Health and Human Development

Laboratory of Developmental Neurobiology—
Phillip G. Nelson, M.D., Ph.D.

Research in neurobiology is conducted using tissue cultures of normal and neoplastic nerve and muscle and various invertebrate preparations. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress. The membrane mechanisms of action of some neuroactive peptides are under investigation.

Office of the Scientific Director—

- Section on Growth Factors—
  Gordon Guroff, Ph.D.

Investigators in this section are interested in the biochemical and physiological actions of nerve growth factor. This factor has been studied for many years and its function is now clear: it is required for the development and survival of the sympathetic and sensory nervous systems. Without nerve growth factor, these neurons die. The chemistry of nerve growth factor has been completely elucidated, but its mechanism of action, and indeed the mechanisms of action of the more than 30 other growth factors now known, are only dimly perceived.

This group's work involves a dissection of the biochemical events, particularly those in the nucleus, which follow the interaction of nerve growth factor with the cell. The systems used are organ cultures of sympathetic ganglia from neonatal animals and the PC12 cell, a pheochromocytoma clone which differentiates *in vitro* into a sympathetic neuron in response to nerve growth factor. In recent years, it has become clear that phosphorylative changes in the proteins of these cells are pivotal events in the actions of the factor. The laboratory is working to isolate and purify the proteins involved and the enzymes carrying out these phosphorylations, as well as to understand the role of these proteins in the structure and transcription of the DNA. The ultimate goal is to define the exact molecular mechanism of these peptide factors. Research is also in progress on the induction of transmitter-synthesizing enzymes, the relationship between the sympathetic nervous system and the immune system, the enzymology of neurite development, and the actions of growth factors on the central nervous system.

- Section on Neuroendocrinology—
  David C. Klein, Ph.D.

Investigations within this section focus on the molecular mechanisms through which hormones and biogenic amines regulate gene expression, using cultured pineal cells as the primary experimental model. Research is concerned with the relationship between biogenic amines and the production and release of hormones; emphasis is given to the study of β-adrenergic control of cyclic AMP and α-adrenergic control of cyclic GMP in pineal cells, and how these systems control metabolism. In addition, enzyme induction and activation are studied using drugs as biochemical and electrophysiologic tools to understand the intracellular reactions involved in large changes in enzyme activity. A second major area of interest is the regulation of circadian rhythms. Current investigations are concerned with the central neural mechanisms involved in generating daily rhythms in primates.

Laboratory of Theoretical and Physical Biology—
David Rodbard, M.D.

This laboratory studies receptors for hormones and neuropeptides *in vitro*, and analyzes pharmacokinetic processes *in vivo* using stable isotopes with liquid chromatography-mass spectrometry. The Section on Theoretical Biology studies drug-receptor interactions, combining experimental and computer-modeling approaches, including computer-assisted optimization of experimental design. The complex opiopeptide receptor system is the present focus of attention.

The Section on Metabolic Analysis studies the metabolism of calcium, other metals, carbohydrates, steroids, and amino acids in humans to evaluate metabolic correlates of growth and development (e.g., effects of growth hormone, sex steroids, and pregnancy).

The Section on Macromolecular Analysis develops new methods for fractionation of proteins and polypeptides, using electrophoretic and other physical-chemical methods.

Laboratory of Neurochemistry and Neuroimmunology—
Harold Gainer, Ph.D.

This laboratory investigates the biosynthesis, secretion, and mechanisms of action of various biologically active neuropeptides. These peptides include ACTH, α-MSH, β-endorphin, dynorphin, vasopressin, and oxytocin. Techniques employed include immunochemistry, immunoassay, immunocytochemistry, recombinant DNA methodology, protein and peptide separation and chemistry, and microchemistry of small brain areas. The laboratory uses a cell-biological approach to the intracellular and extracellular mechanisms which determine the expression of specific neuronal identify (i.e., its endogenous peptides, its particular projection pathways, and its specific termination sites in the central nervous system). The interactions between catecholamine and peptide synthesizing neurons in the nervous system are studied.

Developmental Pharmacology Branch—
Daniel W. Nebert, M.D.

This branch investigates the interplay between genetic and environmental factors affecting drug-metabolizing enzymes. Molecular genetics and recombinant DNA technology are used to exploit the genetic regulation of drug-metabolizing enzymes among inbred mouse strains and in cultured cells. The induction of these enzymes by drugs and other environmental agents, combined with the underlying genetic predisposition of the individual animal, produces diverse responses seen in the research areas of pharmacology, toxicology, teratology, and chemical mutagenesis and carcinogenesis. Data obtained from these experimental test systems are used to develop assays for predicting human populations that are at increased risk for environmental diseases.

National Institute of Dental Research

Neurobiology and Anesthesiology Branch—
Ronald Dubner, D.D.S., Ph.D.

This branch conducts studies on the neural basis of somatic sensation with emphasis on pain mechanisms. Neurocytochemical studies examine the neuronal circuitry in the medullary and spinal dorsal horns utilizing immunocytochemical and autoradiographic techniques at the light and electron microscope level to identify putative neurotransmitters localized to these regions. Elecrophysiologic studies are concerned with the functional characteristics of single cells in the dorsal horn and their role in the coding of pain, temperature, and tactile information. In behavior studies, monkeys are trained to discriminate noxious and innocuous thermal stimuli, and behavioral events are correlated with single-unit activity in the dorsal horn. The effects of opiates, monoamines and other putative neurotransmitters in the brain on neural function and animal behavior are studied utilizing this behavioral model.

The clinical program of this branch conducts research on pain assessment and evaluates various pharmacologic agents utilized in the control of acute and chronic pain. Present studies include the role of endogenous opioid compounds in stress and analgesia, the mechanism of action and efficacy of tricyclic antidepressant drugs in the control of painful neuropathies, the efficacy of different opiate receptor agonists in the treatment of cancer pain, and analgesia potency of non-steroidal anti-inflammatory drugs.

National Institute of Environmental Health Sciences

This institute is the only one of the 11 Institutes that comprise the National Institutes of Health that is not situated on the campus in Bethesda, Maryland. It is located in Research Triangle Park, North Carolina.

Laboratory of Environmental Biophysics—
Colin F. Chignell,Ph.D.

Research programs of the laboratory cover two main areas: the biological effects of some of the physical factors (nonionizing radiation, noise, and light) present in the environment, and the use of physiocochemical techniques to monitor the interaction of chemical and physical agents with various biological systems. The aim of the nonionizing radiation program is to develop new microwave exposure systems and to determine the effect of microwave exposure on human health. Current efforts include the effects of microwave radiation on the central nervous system, the cardiovascular system, the immunologic defense systems, the fetus, and animal behavior. The major goals of the noise program are elucidating basic mechanisms of noise-induced hearing loss, providing better methods for assessing such losses, and providing themeans for accurately reproducing specific noise exposure environments. The program also focuses attention on the reproductive, teratogenic, cardiovascular, and behavioral effect of noise. The light program is concerned with the mechanism of chemically-induced photosensitivity and photoallergy. The effect of light of different wavelengths on the behavior and response of experimental animals to chemical agents is also being examined.

The program in molecular biophysics mainly focuses on the use of sophisticated spectroscopic techniques (ESR, NMR, fluorescence and absorption spectroscopy, CD) to monitor the interaction of environmental agents with biologic systems. Current studies include the generation of free-radical intermediates during the metabolism of xenobiotics, the mechanism of mast cell degranulation, the binding of dyes to nuclei acids, and the interaction of metal ions with proteins and membranes.

Laboratory of Pharmacology—
James R. Fouts, Ph.D.

The research programs in this laboratory are concerned with relationships between the metabolism and translocation of chemicals and toxicity in various target organs. Pharmacologic, biochemical, physiologic, and pharmacokinetic concepts are used to elucidate the mechanisms by which environmental contaminants exert their toxic effects. A special area of emphasis covers those enzyme systems involved in the formation and detoxication of reactive metabolites, such as epoxides. An integrated approach is used in these studies and experiments are performed with purified enzymes (e.g., various cytochromes P-450), enriched cell populations isolated from several organs, isolated perfused organs, and intact animals. Other topics of interest are the mechanisms whereby chemicals with hormonal activity alter the normal functions of the liver; the role of membrane structure and function in the excretion and toxicity of environmental pollutants; and the elucidation of reliable endpoints for the extrapolation of dose-dependent chemical effects across animal species and to humans.

The Laboratory of Pharmacology also serves as a focal point within NIEHS for marine and freshwater biomedical research. This program is especially interested in the direct impact on human health of pollutants present in the aquatic environment (including contaminants present in aquatic animals) as well as in drinking water. Mechanistic aspects of the accumulation, biotransformation, excretions, and toxicity of contaminant chemicals are studied in aquatic vertebrate and invertebrate species, and are compared to similar processes in mammals. Dr. John B. Pritchard heads a program that is situated at the C.V. Whitney Marine Laboratory of the University of Florida near St. Augustine.

Laboratory of Reproductive and Developmental Toxicology—
Robert L. Dixon, Ph.D.

Scientific efforts are directed toward the understanding of mechanisms of reproductive, endocrinologic, and developmental toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis using *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratogenic potential; determine the molecular mechanisms underlying cellular differentiation; study the effects of environmental agents on endocrine function; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the gestational origin of subtle toxic effects which do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of reproductive, endocrinologic, and developmental toxicity using *in vitro* cells and tissues, lower animals, and biochemical test systems.

- Experimental Teratogenesis Section—
  Robert M. Pratt, Ph.D.

Studies in this section deal primarily with embryonic and fetal development and with the mechanisms by which various environmental agents and drugs interfere with normal development. Emphasis is placed on the developent of the craniofacial region and the biochemical and molecular bases for sensitivity to teratogens using cell, organ, and whole embryo culture in conjunction with biochemical, morphologic, pharmacologic, and toxicologic approaches. Of special interest is the manner in which various hormones and growth factors influence normal and abnormal development of embryonic and fetal tissues. Also of interest are the biochemical and molecular factors predisposing various strains of mice to the teratogenic and toxicologic effects of agents such as steroids and dioxins (TCDD).

Laboratory of Behavioral and Neurological Toxicology—
Clifford L. Mitchell, Ph.D.

The research programs of the laboratory are aimed at understanding neuronal plasticity and nervous system mechanisms responsible for adaptation to the environment. This is of particular relevance to toxicology since interference with adaptive mechanisms gives rise to the signs and symptoms produced by a toxicant. An interdisciplinary approach to these problems is taken utilizing behavioral, neurochemical, neurophysiologic, and neuropathologic techniques. Particular emphasis is placed on the behavioral, neurochemical, and electrophysiological indices of neural plasticity and adaptation during the development of the nervous system, and their alteration by exposure to environmental agents. Among the substances being studied are heavy metals, organochlorine pesticides, microwaves, and their interactions with psychoactive drugs.

Laboratory of Pulmonary Function and Toxicology—
Paul Nettesheim, M.D.

The research programs of the Laboratory of Pulmonary Function and Toxicology are concerned with the study of the cellular and biochemical basis of normal and abnormal lung functions. Special areas of emphasis are: (1) regulation of biosynthesis and secretion of mucus glycoproteins; (2) metabolism of prostaglandins in the lungs and the effect of prostaglandins on some metabolic functions of the lung; (3) the composition, secretion, and function of the noncellular alveolar lining layer, particularly its protein components, and disturbances of the acellular alveolar lining layer in disease; (4) the biology, life cycle, and function of respiratory tract epithelial cells studied with *in vivo* and *in vitro* techniques; (5) the mechanisms of toxicity of airborne particles and fibers on lung tissues and the mechanisms of toxicity of asbestos studied *in vivo* and *in vitro*; and (6) mechanisms of respiratory tract carcinogenesis, the development of neoplastic disease, *in vitro* epithelial cell transformation and promotion studies, and mechanisms of cocarcinogenesis and promotion.

National Institute of Mental Health

Laboratory of Clinical Science—

- Section on Pharmacology—
  Julius Axelrod, Ph.D.

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory also engages in examining control mechanisms of the biochemistry of the pineal gland, methylation reactions, and membrane structure and function.

- Section on Clinical Psychopharmacology—
  Juan M. Saavedra, M.D.

The current research program focuses on two areas. One relates to the central mechanisms involved in the control of cardiovascular function and the development of high blood pressure. A combination of microanatomical techniques, radioenzymatic assays, and radioimmunoassays is used to study the metabolism of biogenic amines and neuropeptides in selected brain areas of several animal models of experimental and genetic hypertension.

The second area of interest relates to the role of biogenic amines and neuropeptides in anterior, intermediate, and posterior pituitary function. Both experimental and genetic animal models are used. Current research examines the role of protein carboxylmethylation in the mechanism of vasopressin release, the interactions between biogenic amines, vasopressin and other neuropeptides in the posterior pituitary, and the interactions between somatostatin, α-MSH, estrogens, and catecholamines in the intermediate pituitary lobe.

- Section on Histopharmacology—
  David M. Jacobowitz, Ph.D.

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic), cholinergic, gabaminergic, and peptidergic neurons in the brain, and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical, neurochemical, and physiologic analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying basis for behavioral changes. Catecholamine histofluorescence, immunofluorescence, drugs, stress, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Neuronal amines, enzymes, proteins, and peptides are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence methods are also being used to study the localization of enzymes (DβH) and peptides (a-MSH, CRF, secretin, enkephalin, substance P, pancreatic polypeptide) in the brain.

Laboratory of Cell Biology—
Michael J. Brownstein, M.D., Ph.D.

The members of this group want to locate peptidergic neurons in the CNS and to characterize them anatomically. In addition, they want to learn how peptidergic neurons synthesize, transport, store, and release their biologically active products. The investigators hope to show how these processes are regulated by hormones and neurotransmitters at the transcriptional, translational, and post-translational levels.

- Unit on Biochemical Pharmacology—
  Martin Zatz, M.D., Ph.D.

Current work is on problems in two areas: one concerns the mechanisms by which circadian rhythms are generated and regulated, and the regulation of membrane lipid metabolism by light and neurotransmitters. Related topics include inositidyl metabolism, cyclic nucleotides, photoreception, and the pineal gland. Biochemical and pharmacologic approaches to these problems are emphasized.

Laboratory of Cerebral Metabolism—

- Section on Developmental
  Neurochemistry—
  Louis Sokoloff, M.D.

Laboratory investigations are directed toward the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry to whole-animal physiology. Present emphasis is on the applications of a method recently developed in this laboratory that permits measurement of the rates of cerebral glucose consumption in the structure and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pathologic states.

Laboratory of Preclinical Pharmacology—
Erminio Costa, M.D.

This laboratory conducts a program of research in neurochemical pharmacology directed to elucidate the molecular mechanisms that regulate production, metabolism, and action of various putative neurotransmitters and the mode of action of various psychoactive drugs. Current research includes: the molecular regulation of postjunctional receptors for catecholamines, serotonin, GABA, acetylcholine, and polypeptides; the modification of the interactions between the neurotransmitters and endorphins and other neuropeptides elicited by long-term treatment with drugs; the use of stable isotopes to measure the turnover rate of acetylcholine, norepinephrine, dopamine, serotonin, and GABA by mass fragmentography in brain nuclei; the study of the mechanisms involved in the transsynaptic regulation of gene expression in neural cells; and the study of the heterogeneity of polypeptide neuromodulators in central and peripheral stores as an approach to understanding the regulation of their dynamic equilibrium.

- Section on Biochemical Pharmacology—
  Nortn H. Neff, Ph.D.

The concern of this section is with the effect of drugs on the biochemistry and physiology of the nervous system. Emphasis is placed on the biogenic amine-containing neuron. Current studies are directed toward the characterization of enzymes involved in amine metabolism, the biochemical evaluation of receptor responses, the evaluation of the mechanism of action of drugs that alter neuronal function, and the possible role of the biogenic amines in various disease states.

Laboratory of Preclinical Pharmacology—

- Section on Neuroendocrinology—
  Alessandro Guidotti, M.D.

This section studies the molecular processes whereby neuroendocrine systems adapt and are regulated in response to physiologic and pharmacologic stimuli. Particular emphasis is given to synaptic mechanisms which bring about the secretion of polypeptide hormones, neuropeptides, and catecholamines from the adrenal medulla and pituitary. In both instances, the focus is on postsynaptic processes and on the supramolecular organization of transmitter receptors. These are viewed as plastic units for the regulation of cell function. Interactions of primary transmitters and cotransmitters at synapses are studied as the regulatory events that bring about receptor sub- and supersensitivity. Transmitter-mediated regulation of metabolic events and regulation of gene coding for inducible enzymes and neuropeptides in postsynaptic neuronal cells are examined as a basis for describing memory, behavior, and aging in terms of biochemical and metabolic events.

Primary tissue cultures, neuroblastoma cell lines, and isolated pituitary cells are frequently part of the experimental design. Immunoassays are used to measure the release of polypeptide hormones; reverse phase high pressure liquid chromatography is used to identify and purify new active peptides or their metabolic products; immunochromatography is used to study the regulation of protein synthesis; and enzyme induction, phosphorylation, and other covalent modifications of enzyme function are frequently investigated. Recombinant DNA technology is now being applied to study the regulation of genes coding for inducible enzymes and their substrates.

- Group on Physical Methods—
  James L. Meek, Ph.D.

This group studies neurotransmitter metabolism. The approaches taken include measurement of changes in transmitter content and turnover elicited by drugs or lesions and study of routes of biosynthesis and degradation. Work has involved GABA, glutamate, aspartate, acetylcholine, serotonin, met^5 enkephalin, and cholecystokin. The major technique employed is high pressure liquid chromatography, with fundamental work undertaken as necessary to improve the separation and detection capabilities of this technique for neurotransmitters and their metabolites.

- Section on Neuropeptides—
  Hsiu-Ying T. Yang, Ph.D.

This section is concerned with research on the neuropeptides in the brain and peripheral nervous system. Current studies are on the characterization of the enzymes involved in the metabolism of enkephalin and related peptides. Based on the characteristics of these enzymes, their inhibitors are searched for and used to aid in exploring the role of endogenous opioid peptides. The role of endogenous opioid peptides in analgesia, the mechanism of morphine tolerance, and the interaction of opiates with other neuropeptides are also being investigated.

Laboratory of Neurochemistry—
Seymour Kaufman, Ph.D.

The main effort of this laboratory is devoted to the metabolic interaction between the brain and its peripheral environment. Current research involves: molecular characterization of phenylalanine, tyrosine, and tryptophan hydroxylases, enzymes that are rate-limiting in the catabolism of phenylalanine and the biosynthesis of catecholamines and serotonin, respectively; investigation of the regulation of these enzymes by cyclic nucleotide and calcium-dependent protein phosphorylation; studies on the regulation of tetrahydrobiopterin biosynthesis; and the elucidation of physiologic roles for this compound other than as the essential cofactor for the aromatic amino acid hydroxylases mentioned above; evaluation of the efficacy of pterin administration as therapy for human subjects with disorders of tetrahydrobiopterin metabolism; and determination of the biochemical basis for hypertrophy of muscle, a tissue that shares many cellular characteristics with brain tissue. This work encompasses numerous fields including pharmacology, enzymology, protein chemistry, pterin chemistry, and physiology. In use are techniques as diverse as affinity chromatography, HPLC, brain lesions, and indwelling catheterization of veins and arteries. Experimental preparations include tissue slices, synaptosomes, organ and tissue cultures, hepatocytes, and purified enzymes.

Laboratory of General and Comparative Biochemistry—
Werner A. Klee, Ph.D.

The major emphasis of the current program is directed toward the elucidation of the mechanisms of action of opiates and the peptides that normally interact with opiate receptors. Included are studies on the isolation and characterization of opiate receptors and the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily by purified systems and neuronal cells in culture, are aimed at understanding opiate tolerance and dependence in biochemical terms. In addition, the interrelationships among the several components of inhibitory-receptor adenylate cyclase couples, including especially GTP binding and hydrolyzing proteins, are being explored. The relevance of this work to the action of other CNS-active drugs and to normal brain function is also being explored.

Biological Psychiatry Branch—
Agu Pert, Ph.D.

This laboratory is concerned with analyzing the mechanisms of action of psychoactive drugs and neuropeptides in the brain and defining the neurochemical coding of brain circuits that control specific behaviors. Methods used include extracellular single-cell recording as well as iontophoretic techniques with drugs in specific brain regions. Lesion and microinjection procedures are then utilized to relate these effects to behavior. Current emphasis is on two projects: the actions of endorphins and enkephalins on brain function, especially the processing of pain information; and the effects of lithium (a therapeutic agent in manic-depressive illness) on neurotransmitter receptors sensitivity.

Clinical Neuroscience Branch—
Steven M. Paul, M.D.

- Section on Preclinical Studies—
  Steven M. Paul, M.D.

The major research interests of the section concern the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with neuronal membranes, including membrane receptors and ion channels. Wherever possible, basic laboratory studies are applied to behavioral and clinical problems. Several receptor systems are currently under investigation, including receptors for benzodiazepines, tricyclic antidepressants, serotonin, adenosine, and the neuropeptide cholecystokinin. The roles and regulation of these systems are investigated by: (1) biochemical and pharmacologic characterization of the recognition sites; (2) isolation and characterization of the endogenous modulators of these sites; (3) development of appropriate *in vitro* models for studying these receptors (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharmacologic experiments in animals; (6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor changes in correlation with the behavioral manifestations of these genetic mutations; and (7) post-receptor events, including calcium transport and cyclic nucleotide changes.

- Section on Brain Biochemistry—
  Candace B. Pert,Ph.D.

It has recently become apparent that neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell surface receptor. This section uses radiolabeled ligands with fully preserved biological activity to study drug and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain tissue in which neuroanatomical relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus with emphasis on identifying opiatergic neurocircuitry, systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (e.g., angeldustin, bombesin, substance P, neurotensin, and CCK) are also being studied. In short, the thrust of the laboratory's efforts is the characterization, measurement, visualization, and solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally.

National Institute of Neurological and Communicative Disorders and Stroke

Developmental and Metabolic Neurology Branch—

- Membrane Biochemistry Section—
  Peter H. Fishman, Ph.D.

This section research involves the biosynthesis, organization, and function of cell surface membrane components. Of major interest are the mechanisms by which cells receive, process, and attenuate external signals. The hormone-stimulated adenylate cyclase system is used as a model for transmembrane signaling. Hormones are recognized by specific receptors on the external side of the plasma membrane; following hormone binding, there is a transduction process which leads to stimulation of adenylate cyclase on the cytoplasmic side of the membrane. Prolonged stimulation results in desensitization, where the transduction process becomes attenuated and in down-regulation, where the receptors become internalized and degraded. The laboratory is also exploring the biosynthesis of two classes of receptors, glycoproteins and glycolipids; how these receptors become integrated into the plasma membrane; how the receptors are turned over; and how the cell regulates these processes.

Experimental Therapeutics Branch—

- Biochemical Neuropharmacology
  Section—John W. Kebabian, Ph.D.

The Biochemical Neuropharmacology Section studies the biochemical mechanisms underlying the activity of receptors for neurotransmitters. There is a special interest in dopamine receptors found in brain and simpler peripheral endocrine tissues. In the recent past, the section has studied the D-2 dopamine receptor in the intermediate lobe of the rat pituitary gland. The knowledge obtained from simple endocrine tissues about the biochemical mechanisms underlying receptor function has been applied to the brain.

- Physiological Neuropharmacology
  Section—
  Judith R. Walters, Ph.D.

Studies in the Physiological Neuropharmacology Section are focused on investigation of neuronal interrelationships and drug interactions with neurotransmitter function in the CNS, especially in areas of the basal ganglia, including the substantia nigra, striatum, and globus pallidus. Extracellular single-unit recording procedures and iontophoretic techniques are chiefly employed; brain slice preparations are being established. Currently, the functions of dopamine, GABA, and peptide-containing neurons in these brain regions are being investigated through neurophysiologic determinations combined with drug treatment, administration of selective lesions, and assessment of biochemical parameters of transmitter function.

Laboratory of Neuropathology and Neuroanatomical Sciences—

- Section on Cellular Neuropathology
  Henry DeF. Webster, M.D.

This section uses morphological, immunocytochemical, virologic, biochemical, and immunologic methods to study cellular mechanisms of myelin formation, maintenance and breakdown. Special emphasis is placed on how these mechanisms relate to the diagnosis and pathogenesis of human demyelinating diseases. The section also investigates drugs and toxic agents that affect myelin sheaths and myelin-forming cells.

Laboratory of Neurophysiology—
Jeffery L. Barker, M.D., and Thomas G. Smith, Jr., M.D.

The principal aim of this laboratory is a multidisciplinary analysis of the cellular properties of specific CNS neurons and the pharmacologic effects of clinically important drugs on these properties. Most of the research is conducted using monolayer cultures of neurons dissociated from different regions of the embryonic CNS. The methods employed are primarily electrophysiologic, including intracellular recording, voltage-clamp, and patch-clamp techniques, although other methods, including biochemical and morphologic, are also utilized. Specific projects include the comparison of chemically and electrically excitable membrane properties in CNS neurons and the effects of clinically important drugs on these properties, the identification of specific cell types using immunohistochemical and biochemical methods, and the separation of specific populations of neurons using fluorescence-activated cell sorting techniques.

National Institute of Mental Health

Alcohol, Drug Abuse, and Mental Health Administration

Herbert Pardes, M.D.,
Director
Frederick K. Goodwin, M.D.,
Director, Intramural Research
Dennis L. Murphy, M.D.
Associate Director for Clinical Research
Seymour Kety, M.D.
Associate Director for Basic Research
Rex W. Cowdry, M.D.,
Acting Clinical Director

The National Institute of Mental Health (NIMH) offers an opportunity for postdoctoral research training in psychiatry and in the biologic and behavioral sciences. The NIMH intramural program is located on the NIH campus in Bethesda, Maryland, and in the William A. White Building, St. Elizabeths Hospital, Washington, D.C. Some medical staff fellows conduct clinical and/or basic research, and are responsible for the clinical care of patients admitted for research and therapeutic purposes. Other fellows engage primarily in laboratory research in the biologic or behavioral science laboratories under the preceptorship of the senior staff. All medical fellows participate in tutorial seminars and other teaching programs as their needs and desires indicate. Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all medical staff fellows to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Appointments in Clinical Research

The NIMH recruits about 12 new medical staff fellows each year who are primarily involved in clinical research. Appointments normally begin July 1 and are usually for 2- or 3-year periods, although in some instances they may be extended.

Fellows usually begin their appointments after the PGY-4 level of residency training. Well-qualified individuals, however, may be appointed after PGY-2 or PGY-3 levels of residency training in psychiatry, neurology, or other clinical specialties. The Clinical Center is approved for 1 year of psychiatric residency training at the PGY-4 level.

Applications for the Medical Staff Fellowship Program are now being accepted only for July 1986 appointments. Since selections for these positions will be made in January 1985, PGY-2 or PGY-3 psychiatric residents may now apply.

Medical staff fellows usually work in close association with senior clinician-scientists on one of the clinical research wards or in a clinical research laboratory. The first year is usually predominantly clinical with intense experience in the diagnosis and inpatient management of research patients, special clinical and administrative issues in a research setting, psychopharmacology, clinical research methodologies and design (by the initiation of at least one clinical research project under the direction of the senior clinician-scientist), and the psychotherapy and psychodynamics of research patients and their families. The following years focus primarily on research that may be clinical, clinical-biochemical, or laboratory, depending on the interests of the fellow and the status of the clinical research program. Intensive clinical supervision on the inpatient psychiatric unit is available from senior psychiatrists. Candidates desiring more information about clinical fellow positions should write to Rex W. Cowdry, M.D., NIMH, Building 10, Room 3N234, National Institutes of Health, Bethesda, MD 20205.

Appointments in Laboratory Research

Some fellows work primarily in the laboratory under the preceptorship of a senior staff scientist. They are usually assigned to a basic science laboratory for intense training and experience in specific neurobiologic or psychosocial concepts and methodologies. For further information about these positions in the neurobiologic area, contact the chief of the particular basic science laboratory or section at the National Institutes of Health, Bethesda, Maryland 20205. For information in the psychosocial area, contact Marian Yarrow, Ph.D., NIMH, Building 15K, National Institutes of Health, Bethesda, MD 20205.

Medical Staff Fellows in Pharmacology (PRAT)

Some of the NIMH programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in preclinical or clinical pharmacology. For more information about the PRAT program, see page 85.

Clinical and Basic Research Branches

Biological Psychiatry Branch—
Robert Post, M.D.

This branch conducts a broad program of research, training, and treatment of clinical psychiatric problems including manic-depressive and schizo-affective illness, panic-anxiety disorders, menstrually related mood disorders, and suicidality. The focus of the branch is psychobiologic and brings together information from the following disciplines—psychiatry, psychology, neurology, genetics, pharmacology, and biochemistry. Longitudinal evaluation of the course of illness and response to treatment is an important clinical and research methodological approach. Some specific research interests are psychogenetics, the biochemistry of neurotransmission, neuroendocrinology, investigations of perception and cognition, cerebral tomography of average evoked potentials, and positron tomography. A general goal of this branch is to develop programs to investigate psychologic, biochemical, and neuroanatomic contributions to the study of manic-depressive illness, anxiety disorders, and related symptoms.

Fellows will be trained in clinical research methodology, data analysis, and clinical management of research patients.

Opportunities are also available for studying behavioral and biochemical laboratory techniques with Drs. Agu Pert and Paul Marangos.

- Section on Psychobiology
  Robert M. Post, M.D.

This 14-bed psychiatric research unit focuses on the clinical and biologic assessment and treatment of patients with manic-depressive and schizo-affective illness and rapidly cycling phenomena. Medical staff fellows are research collaborators in a variety of studies of the interactions of psychological and biologic parameters in the psychoses and usually take responsibility for the design, conduct, and publication of several research projects. Mood, cognitive, and behavioral variables are viewed in relation to such biologic correlates as sleep, motor activity, evoked potentials, and endocrine function. Particular attention is given to the study in psychiatric patients of central amine metabolism with the use of CSF strategies, such as the measurement of amine metabolites, cyclic nucleotides, regulatory enzymes, and peptides in CSF. Work is closely coordinated with several biochemical laboratories. The mechanisms and time course of the biologic effects of psychotropic drugs are studied in relation to clinical response.

New pharmacologic agents are being tested, including noradrenergic receptor agonists, anticonvulsants such as carbamazepine, and several endogenous polypeptides. The mechanisms underlying the paradoxic antidepressant effect of one night's sleep deprivation are being studied. Clinical and laboratory studies of psychomotor stimulants are ongoing. An active behavioral pharmacology laboratory is maintained for the study of the long-term effects of psychomotor stimulant administration and electrical kindling in rodents and primates as models for the development of psychosis. Dr. Agu Pert also conducts major programs on behavioral pharmacology, *in vivo* receptor autoradiography, and the interaction of peptide and neurotransmitter mechanisms.

- Section on Neuroendocrinology
  Philip W. Gold, M.D.

The work of the section on Neuroendocrinology is conducted in three settings. First, on the clinical research unit of the Biological Psychiatry Branch, neuroendocrine studies in patients with affective illness and normal controls focus on corticotropin releasing factor and its interactions with other peptides, particularly the endogenous opiates and the neurohypophyseal hormones, arginine vasopressin and oxytocin. A second setting is the clinical research unit of the Developmental Endocrinology Branch of the NICHD, which studies clinical neuroendocrine disorders such as Cushing's disease, Addison's disease, and various conditions characterized by hypothalamic-pituitary gonadal dysregulation. Members of the section make rounds on this ward and participate in active collaborative research. A particular focus is the study of the pathophysiological analogies between Cushing's disease and depression. The third setting is the Preclinical Laboratory, which has an active program to measure a variety of neuropeptide hormones, including CRF, ACTH, β-endorphin, arginine vasopressin, and oxytocin, and which conducts studies of neuroendocrine regulation in laboratory animals and subhuman primates. Each associate will spend considerable time in each of these settings in order to have a well-rounded experience in the scope and techniques of psychoneuroendocrinology.

- Unit on Anxiety and Affective Disorders—Thomas W. Uhde, M.D.

This unit is engaged in the clinical and laboratory study of patients with anxiety and affective disorders. Most clinical research is conducted in the new Ambulatory Care Research Facility (ACRF), although intensive diagnostic assessment and drug treatment is available to patients on the 14-bed inpatient unit of the Biological Psychiatry Branch. A major emphasis is on the phenomenology, life course, familial patterns, and psychobiology of panic disorder, including agoraphobia with panic attacks. Particular attention is given to the study of possible "state" or "trait" markers of pathological anxiety and the testing of new anxiolytic agents. Current biologic correlates of interest include galvanic skin response, evoked potentials, sleep architecture, pain sensitivity, ^{3}H-imipramine an ^{3}H-dihydroergocryptine binding to the platelet and the neuroendocrine responses to agents with relatively selective effects on noradrenergic and other neurotransmitter systems. Drugs currently under study include alprazolam, caffeine, carbamazepine, clonidine, diazepam, propranolol, RO 15-1788, and yohimbine.

- Unit on Peptide Studies—David R. Rubinow, M.D.

This unit is involved in investigating basic mechanisms and clinical manifestations of endocrine and peptide effects on mood, cognition, and behavior. The interface between medicine and psychiatry is explored in a variety of inter-Institute collaborative research projects established through the NIMH consultation-liaison service. An additional major focus is the biological characterization and treatment of menstrually-related mood disorders.

Clinical Neuropharmacology Branch— Dennis L. Murphy, M.D.

This branch conducts clinical and laboratory studies designed to contribute to the understanding of the mechanisms of therapeutic drug effects in individuals with affective disorders, obsessive-compulsive symptoms, dementias, and other behavioral disorders. The studies are primarily based on a 10-bed psychiatric research ward. The in-patient investigations are complemented by an outpatient program for the longer-term study of obsessive-compulsive and dementia patients.

Support for the clinical studies includes a biochemistry/neuroendocrinology laboratory and a behavioral assessment and data processing program. Other neurochemical laboratory studies are oriented toward molecular pharmacology using biophysical techniques such as NMR (Jonathan Costa, M.D., Ph.D.). Facilities for nonhuman primate studies (directed by Thomas Insel, M.D.) and studies of drug effects in small animals are also available in the branch.

The ward research investigations, which are balanced between biologic-pharmacologic and psychologic-phenomenologic approaches, take place in the setting of an active clinical treatment program. The incoming medical staff fellow, depending on his or her prior research and clinical experience, will usually participate at first in ongoing research projects and the clinical program. With increased experience, the fellow will work with a senior staff member in the planning, design, and implementation of one or more research projects to be initiated in the first year and completed in the second or possibly third year.

Emphasis is on the strategies and methods used in clinical research and laboratory approaches to clinical problems. Specific research projects range from psychobiological studies of the characteristics of individuals who do or do not respond to specific drugs and to laboratory or animal studies of the effects of drugs on cellular processes, including enzyme activity, membrane transport, and neurotransmitter receptor functions. Studies of psychoactive drug effects on neurotransmitter metabolism and neuroendocrine function are a particular focus in both the clinical and nonhuman primate areas.

Drugs currently under study include selective monoamine oxidase inhibitors, some natural precursors of brain neurotransmitters, and lithium carbonate, as well as other antidepressants and some new investigational compounds. Special areas of study at present include investigations of adaptational responses to long-term drug administration in neurotransmitter receptors and secondary effector systems; animal models of affective disorders; neuroendocrine responses, and other characteristics differentiating subgroups of psychiatric patients; studies of monoamine oxidase; the development of new electron microscope-based techniques (e.g., energy loss spectroscopy) for the study of the storage and metabolism of neurotransmitter amines and other substances in cells; and methods for the assessment of behavioral and psychological states.

Clinical Psychobiology Branch—
Thomas A. Wehr, M.D.

Clinical research is conducted in areas related to affective illness (depression and mania) and sleep disorders. Laboratory research involves studies of the neurobiology of sleep and circadian rhythms. Structurally the branch is divided into the Clinical Research Unit, the Unit on Sleep Studies, and the Outpatient and Follow-up Unit. Throughout the 2- to 3-year assignment, the fellow's time is divided among clinical care-ward management, clinical research, and laboratory research, depending on interest. Direct responsibility for research projects is assumed from the beginning.

- Clinical Research Unit—
  Thomas Wehr, M.D.

The unit represents the major research resource of the branch and is located in a 15-bed psychiatric research ward.

The major focus of clinical research on the inpatient unit is the treatment of affective disorders and the investigation of abnormalities in the timing and phase of circadian rhythms in depression, mania, and sleep disorders.

Both pharmacological and nonpharmacological treatment strategies are studied. For example, the effects of antidepressants and thyroid hormone on the cycles of mania and depression are currently being evaluated. Non-pharmacological treatments include sleep deprivation, altering sleep schedules, and manipulation of environmental light. We have the capability of studying similar interventions in normal volunteers and animals. We are evaluating the possible synergistic effects of medications and non-pharmacologic treatments. Neuroendocrine studies involving, for example, the thyroid and adrenal and the effects of light on melatonin secretion are being conducted.

The characteristics of circadian systems in patients and normal volunteers are studied in conditions where they are isolated from all time cues for periods up to 4 weeks. New techniques and instruments make it possible to study continuously changes occurring in motor activity, body temperature and EEG-recorded sleep.

- Outpatients and Follow-up Unit—
  Norman Rosenthal, M.D.

A common theme of both inpatient and outpatient studies is the longitudinal study and treatment of cyclical affective disorders and sleep disorders. Outpatients with affective disorders are followed in the clinic and admitted for psychobiological and treatment studies. We encourage the study and treatment of interesting subgroups. For example, patients who regularly become depressed during certain seasons have been identified and are studied and treated biologically and psychologically.

- Unit on Sleep Studies—
  Wallace Mendelson, M.D.

This unit conducts studies of sleep physiology and pharmacology, with emphasis on the role of sleep in psychiatric illnesses such as depression. Other areas of concern are sleep as a circadian rhythm and primary pathologies of sleep such as sleep apnea syndrome. Psycho-physiologic studies of insomnia and hypersomnia are pursued at a clinical level. Animal sleep studies involve experimentation with possible naturally occurring "sleep factors" and the role of benzodiazepine receptors in sleep and anxiety. Electronic analysis of the EEG is done at both clinical and animal levels.

- Laboratory Studies—
  Gerard Groos, Ph.D.

The basic research program of the Clinical Psychobiology Branch focuses on the neuropharmacologic, electrophysiologic, and neuroanatomic mechanisms that underlie circadian rhythmicity in mammals. To this end, we study the physiology of a putative "biological clock" in the brains of rodents: the suprachiasmatic nuclei. These nuclei are investigated at various levels of analysis. Microelectrode recordings are performed *in vitro* and *in vivo* to study the basic mechanisms of rhythm generation. Lesion studies in freely moving animals enable us to further elaborate the anatomic pathways mediating the regulation of the sleep-wake cycle. Microiotnopheretic techniques are used to define the role of endogenous transmitters in the generation and synchronization of circadian rhythms.

Clinical Neuroscience Branch—
Steven M. Paul, M.D.

The branch conducts a multidisciplinary program in basic and clinical neuroscience and attempts to integrate data on the biochemistry and pharmacology of the central nervous system with an understanding of the pathogenesis and treatment of major psychiatric diseases. Structurally the Neuroscience Branch consists of four sections: Molecular Pharmacology, Preclinical Studies, Brain Biochemistry, and Clinical Studies. Medical staff fellows are assigned to the clinical research unit, usually for a period of 2 to 3 years. During this time their activities are divided between direct patient care, clinical research, and laboratory research, depending on the interests and talents of the individual. Medical staff fellows will be encouraged to become actively involved in ongoing research projects, as well as to develop their own research protocols as early as possible. Collaborations between individual medical staff fellows and the three basic science sections, on both laboratory and clinical research projects, will also be encouraged. The overall goal of the branch is to create a climate in which sound scientific findings can be applied to an understanding of both normal and abnormal behavior.

- Section on Preclinical Studies—
  Steven M. Paul, M.D.

The major interests of the section concern the interaction of psychotropic drugs (minor tranquilizers, antidepressants, sedatives, stimulants, and antipsychotics) with neuronal membranes, including membrane receptors and ion channels. Wherever possible, basic laboratory studies are applied to behavioral and clinical problems. Several receptor systems are currently under investigation, including receptors for benzodiazepines, tricyclic antidepressants, serotonin, adenosine, and the neuropeptide cholecystokinin. The role and regulation of these systems are investigated by: (1) biochemical and pharmacologic characterization of the recognition sites; (2) isolation and characterization of the endogenous modulators of these sites; (3) development of appropriate *in vitro* models for studying these receptors (brain slices, tissue culture); (4) structure-activity studies of chemically modified substances that are related to the naturally occurring ligands; (5) behavioral and pharmacologic experiments in animals; (6) genetic studies in inbred strains of rats and mice, coupled with an examination of receptor changes that correlate with the behavioral manifestations of these genetic mutations; and (7) postreceptor events, including alterations in calcium transport and cyclic nucleotide levels.

- Section on Brain Biochemistry—
  Candace B. Pert, Ph.D.

It has recently become apparent that neurosecretions (neurotransmitters, etc.) and many psychoactive drugs share a common site of initial action—the neuronal cell surface receptor. We use radiolabeled ligands with fully preserved biologic activity to study drug and neurotransmitter receptors not only in membrane preparations, but also on thin slices of unfixed frozen brain where neuroanatomic relationships and even cytoarchitecture are fully preserved. Brain receptors and their endogenous peptide ligands can be readily mapped at the light level using computer-assisted densitometry of autoradiographic films. Opiate receptors and their ligands, the opiate peptides, remain the primary focus with emphasis on identifying opiatergic neurocircuitry, systematic phylogenetic variation, and the biochemistry and morphologic significance of Type 1 (conformationally plastic) and Type 2 (conformationally static) opiate receptors. Other neuropeptides and their receptors (e.g. angeldustin, bombesin, substance P, neurotensin, and CCK) are also being studied. In short, the thrust of our laboratory efforts is the characterization, measurement, visualization, and solubilization of brain receptors as well as other neuronal antigens, located both on the cell surface and internally.

- Section on Molecular Pharmacology—
  Steven M. Paul, M.D., Acting

Current investigations are directed toward an understanding of the regulation and actions of receptors at the cellular level. Two examples of current work are studies of: interactions between GABA receptors and benzodiazepine receptors; the synergistic actions of these receptors on neuronal firing and biochemical parameters of cellular activity and benzodiazepine receptor purification; and mechanisms that control the number and functioning of β-adrenergic receptors in cultured cell lines and alterations in β-adrenergic receptors that occur following exposure of cells to β-adrenergic agonists (desensitization).

- Section on Clinical Studies—
  David Pickar, M.D.

This unit encompasses the entire inpatient evaluation and treatment of patients on the clinical research unit. Current research problems include investigations of the clinical phenomenology of schizophrenia and the similarities and differences between schizophrenia and schizo-affective disorders. Studies on the role of central and peripheral opioid systems (i.e., enkephalin, β-endorphin) in stress, schizophrenia, and depression, and inpatients with acute and chronic pain are also ongoing. Laboratory investigations on possible peripheral biologic markers in schizophrenia, as well as various affective disorders (i.e., platelet [^{3}H] imipramine binding, serotonin transport, RBC membrane fluidity), are being carried out in hopes of unraveling vulnerability factors in these disorders.

Other areas of interest involve attempts to delineate vulnerability markers (state-independent and state-related variables); the prediction of antipsychotic drug response and prognosis; exploration of GABA, neuropeptides (such as endorphins and vasopressin), and other neurotransmitter systems for their potential involvement in psychosis; evaluation of new antipsychotic drugs; assessment of pharmacologic and endocrinologic aspects of schizophrenia and schizo-affective illness; immunologic aspects of schizophrenia; study of CAT scan abnormalities; cognitive and psychophysiologic evaluations; and PET scan studies.

Laboratory of Clinical Science—
Seymour Kety, M.D., Acting

This laboratory conducts research on the biochemistry, physiology, and pharmacology of the nervous system and relates these findings to clinical areas in medicine, neurology, psychiatry, and anesthesiology. Applicants for the medical staff fellow program in laboratory research should have at least 1 year of clinical training, whereas those interested in clinical research are required to have at least 2 years of postdoctoral training in neurology or psychiatry before arrival for duty.

The research program objectives are attained through the cooperative efforts as well as the independent research of investigators in the various sections and units of the laboratory.

- Section on Histopharmacology—David M. Jacobowitz, Ph.D.

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic), and cholinergic and gabaminergic neurons in the brain and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical and neurochemical analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying bases for behavioral changes. The catecholamine histofluorescence method, the study of drugs, stress, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Behavioral studies being pursued involve the genetic fat rate, spontaneous hypertensive rat, sexual and reproductive function and various stress manipulations. Neuronal amines, enzymes, and peptides are measured within specific brain nuclei, tracts, and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence and radioimmunoassay are also being used to study the localization of enzymes (DβH) and peptides (α-MSH, bombesin, enkephalin, vasopressin, substance P, and pancreatic polypeptide) in the brain. Studies of peptides in human and animal brain and cerebrospinal fluid are currently under way. These are designed to examine the dynamics of release of peptides within the brain.

- Section on Analytical Biochemistry-Sanford P. Markey, Ph.D.

The unit develops techniques for clinical studies of neurotransmitters, neurohormones, peptides and their metabolites, and drugs that influence their formation or disposition. Projects include the synthesis of stable isotope-labeled analogs of amines and metabolites for human kinetic studies, the isolation and quantitative assay of compounds of interest, and the design and construction of alternate ion sources for mass spectrometry. Current projects include the synthesis of ^{18}O-dopamine as a probe of peripheral norepinephrine metabolism in humans; the negative ion mass spectral quantitation of levels of melatonin in plasma and its alteration by disease and pharmacologic intervention; and the assay of the major urinary melatonin metabolite for developmental studies in neonates, infants, children, and in patients with disorders of the sympathetic nervous system or who receive drugs influencing the sympathetic nervous system.

- Section on Clinical Pharmacology—William Z. Potter, M.D.

The central focus is the study of the mechanisms of action of antidepressants and other psychoactive drugs using integrated biochemical and pharmacokinetic studies in man and animals. At present, clinical studies involve both patients with affective illness and normal volunteers. New biochemically specific drugs are examined to identify common biochemical effects using measures in cerebrospinal fluid, plasma, and urine. Parallel investigations are done in animals in which more invasive and detailed studies of CNS biochemical alterations are possible. Since the noradrenergic and serotonergic systems can be directly or indirectly implicated in the action of all known antidepressants, the pretreatment noradrenergic and serotonergic "tone" of patients with affective illness is contrasted to that in volunteers and those with other psychiatric illnesses. Techniques include assay of antidepressants, hormones, neurotransmitters, and their metabolites in tissues and body fluids by radioimmunoassay, HPLC, or GC-MS; pharmacokinetic modeling of data in neurotransmitter systems; *in vitro* binding techniques for studying neurotransmitter receptor alterations; and the development of appropriate animal models.

- Section on Experimental Therapeutics—
  David C. Jinerson, M.D.

The section conducts studies of the clinical pharmacology of a variety of neuropharmacologic agents, including clonidine and phencycliding. Neurochemical, neuroendocrine, and pharmacokinetic experiments and drug trials are in progress in a variety of neuropsychiatric and psychosomatic syndromes. The section operates a clinical research unit to pursue these studies. In collaboration with other investigators in the Laboratory of Clinical Science, experiments are in progress in primates and man to measure turnover rates of brain monoamines by stable isotape labeling techniques and changes in synthesis rates produced by disease states and/or pharmacologic treatment. Diseases of interest at the present time include orthostatic hypotension, anorexia nervosa, bulimia, several presenile dementias, and hyperactivity in children.

- Section on Childhood Mental Illness—
  J. L. Rapoport, M.D.

This unit operates on a six-bed day and/or overnight hospitalization inpatient program in collaboration with the Section on Experimental Therapeutics, Laboratory of Clinical Science, and independently on a pediatric ward maintained by NICHD. Current focus is on diagnostic assessment and drug treatment of hyperactive children. Drug studies include pharmacokinetic studies of drugs given to children and studies of kinetics and metabolism of neurotransmitter systems via body fluids.

Also under way are outpatient studies of obsessive-compulsive children, and the evaluation of children whose parents have been hospitalized here in the past for affective illness and offspring of alcoholics.

Clinical Neurogenetics Branch—
Elliot S. Gershon, M.D.

The clinical neurogenetics branch conducts clinical and basic biologic and pharmacologic studies related to the genetics of manic-depressive illness and schizophrenia. Fellowship positions do not open every year, but are considered in terms of the suitability of the applicant to the area in which he or she wishes to work.

- Section on Clinical Genetics—
  Elliot S. Gershon, M.D.

Clinical investigations include biologic, pharmacologic and psychosocial studies, of patients and their relatives, and/or normal controls. Young people at increased risk of illness, and patients currently in remission, are also studied in attempts to define trait markers of vulnerability. Clinical and related basic laboratory studies are pursued in molecular genetics and in neuroscience. Population genetics and pharmacogenetic investigations are also performed. Current projects include genetic studies of DNA polymorphisms, neuron-like characteristics of cultured lymphoblasts and fibroblasts, neuroendocrine and other responses to pharmacologic challenge, and neuropeptides and neurotransmitters in CSF and blood.

- Section on Biochemical Genetics—
  Carl Merril, M.D.

This section concentrates on studies of structural variations in macromolecules in neurobiology, and their possible relation to the etiology of inherited disorders. Investigations of this Section have greatly increased our ability to visualize protein gene products on gels, which have allowed documentation of protein variations in disease states such as the Lesch-Nyhan syndrome. Polymorphic markers for use in genetic linkage studies are also identified by these methods. The application of these methods to proteins of neurobiological interest, such as neurotransmitter receptor proteins and precursor proteins for neuropeptides, is now being undertaken.

Laboratory of Cell Biology—
Michael J. Brownstein, M.D., Ph.D.

The members of this group have a variety of research interests. These include light and electron microscope-level neuroanatomy, chronobiology, developmental neurobiology, biosynthesis of biologically active molecules, isolation of novel peptide hormones, and regulation of intracellular processes by chemical messengers.

- Section on Pharmacology—
  Julius Axelrod, Ph.D.

This section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones; and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory examines control mechanisms of the biochemistry of the pineal gland and membranes.

Laboratory of Developmental Psychology—
Marian Radke-Yarrow, Ph.D.

This program conducts research on the behavioral development of children, primarily affective, social and cognitive development, and on interrelations between stressful conditions—biomedical or psychosocial—and the functioning of children. There is an emphasis on research strategies and methods in the investigation of child behavior. Variables such as mood, aggression, altruism, and social cognition are of special interest. Laboratory studies, as well as field studies, are conducted on children, infants through adolescents. Much of the research is collaborative, involving investigators in other laboratories of NIMH and other institutes. Specific projects include studies of early problem aggression; of developmental continuity and discontinuity in affective, social, and cognitive characteristics of children; and of child rearing environments and their consequences for children. Among the risk groups being studied are children reared by parents with affective disorders. Biomedical conditions studied in relation to behavior include normal developmental changes in adolescence, hormonal abnormalities, and severe physical disease states.

Laboratory of Psychology and Psychopathology—
Allan F. Mirsky, Ph.D.

This laboratory conducts a broad program of basic and clinical research on attention, learning, and memory in both humans and monkeys and on the neurophysiologic and psychophysiologic mechanisms involved in these processes.

Studies on the neurophysiology of attention in monkeys with a single unit recording from various parts of the brain and with stimulation and ablation techniques are focused on the investigation of animal models of cognitive processes that may be impaired in many human psychiatric and neurologic disorders. Parallel studies of cognitive processes in psychiatric and neurologic patients and in normal controls using similar behavioral techniques are designed to permit direct comparison with the animal work.

Studies of memory functioning in a wide variety of patients and of pharmacologic influences on memory in humans are being conducted by Herbert Weingartner, Ph.D. Studies of attention and autonomic nervous system functioning in schizophrenics and in other patients and drug effects on these processes are being done by Theodore P. Zahn, Ph.D. Investigations of attention and cortical and brainstem averaged evoked potentials in psychiatric and neurologic patients are under way.

Laboratory of Neurobiology
Ichiji Tasaki, M.D.

Current research projects include electrophysiologic, biomechanical, and biochemical studies of the mechanism of excitation of nerve cells and fibers. We are using extremely sensitive mechanical devices constructed in the Laboratory of Neurobiology to analyze mechanical changes associated with action potentials in nerves. These changes are interpreted in terms of structural changes in the axolemma-ectoplasm complex of nerve.

Another major project in this laboratory involves a developmental study of the appearance of excitability in nerve and muscle cells grown in culture. This project involves studies of excitability at three levels of cellular organization: binding studies using a variety of toxins known to affect excitability, studies involving the uptake of sodium by the cells in response to a variety of drugs and toxins, and electrophysiologic responses of the cells to various drugs and toxins. The goal of this work is to understand how these cells become excitable and, thus, the biochemical mechanism of excitability.

Laboratory of General and Comparative Biochemistry—
Giulio L. Cantoni, M.D.

Investigations are concerned with the mechanisms and pathways of biological methylation, alkaloid biosynthesis, opioid peptides, cellular differentiation, and gene expression in eukaryotes. The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, mechanism of drug addiction, muscle differentiation in cell culture, and genetic engineering.

- Section of Alkaloid Biosynthesis—
  S. Harvy Mudd, M.D.

This section studies the enzymes involved in biosynthesis in methylation in plants and their control. The section also studies enzymatic mechanisms of transmethylatoin and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

Laboratory of Cerebral Metabolism—
Louis Sokoloff, M.D.

- Section on Developmental Neurochemistry—
  Louis Sokoloff, M.D.

A broad program of investigation is conducted on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds such as hormones that play important physiologic roles in CNS function. A method recently developed in this laboratory permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic, pharmacologic, and pathologic states.

Laboratory of Neurochemistry—
Seymour Kaufman, Ph.D.

The following areas are studied: the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine-hydroxylating system. In addition to studies with the pure enzymes, emphasis is placed on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia. This laboratory investigates the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin, the relationship between the properties of the enzymes, and physiologic regulation of rates of synthesis of these neurotransmitters; the biochemical basis for skeletal muscle hypertrophy, including the effects of exercise and neural factors in the process; cell-surface membrane proteins and receptors in their role in cellular differentiation; and the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

Laboratory of Neurophysiology—
Edward V. Evarts, M.D.

This laboratory combines the techniques of electrophysiology, neuroanatomy, neurotransmitter receptor localization, and experimental psychology in studies aimed at understanding the brain circuits, cell types, and receptor mechanisms relevant to neuropsychiatric illness. Research is organized in four units.

- Unit on Motor Systems—
  Edward V. Evarts, M.D.

This unit is engaged in studies of single nerve cell activity in basal ganglia, cerebellum, thalamus, and mortor cortex of monkeys performing learned movements. The aim of the work is to achieve an understanding of the way in which the activity of these structures is integrated during normal movement and how diseases within these structures impair movement.

- Unit on Dynamic Brain Structure—
  Miles Herkenham, Ph.D.

Traditional neuroanatomical techniques reveal features of static morphology; however, the use of fresh brain cut into sections in the cryostat enables studies of the localization of neurotransmitter and drug receptors, enzymes, 2-deoxyglucose metabolism, and architecture. This unit is engaged in studies of correlative, comparative, and developmental features of opiate receptor localization revealed by autoradiography. Related neurochemical and metabolic markers are visualized to show the interaction of the opiate system with other brain systems during normal development and function, after experimental manipulation or in cases of disease-induced abnormalities.

- Unit on Motor Psychophysics—
  Jerome N. Sanes, Ph.D.

The work in this unit is aimed at applying the principles of motor psychophysics to an understanding of the pathophysiology of clinical disorders including Parkinson's disease, peripheral neuropathy, cerebellar ataxia, tardive dyskinesia, and other conditions with prominent motor impairments. The aim of the work is to obtain more reliable and objective measures for evaluation of long-term efficacy of therapeutic agents as well as to provide information on the basic neural mechanisms relating brain lesions to altered motor behavior. There are close collaborative relations with clinical branches in several different institutes.

- Unit on Cerebral Cortex—
  Steven P. Wise, Ph.D.

Work in this unit combines techniques of basic neurobiology with techniques of single cell recording in operantly conditioned rats and monkeys. The aim of the work is to discover how the different topographic divisions of the sensorimotor cortex interact in behaving organisms. Special attention is devoted to the different sorts of sensory information that are processed in different subdivisions of the sensorimotor cortex and to how behavioral set and intention for future action are reflected in regions such as the premotor and supplementary motor areas of the cerebral cortex. Specialized neurobiologic techniques (e.g., intracellular injection of neuronal markers and laminar electrophysiologic analysis) are carried out in parallel with the behavioral studies.

Laboratory of Brain Evolution and Behavior—
Paul D. MacLean, M.D.

Opportunities are offered for research on evolutionary, developmental, ethologic, and ecologic factors relating to brain function and behavior. Large outdoor and indoor habitats are available for comparative studies on reptiles, birds, and mammals living under seminatural conditions. The laboratories are equipped for neuroanatomic research, microelectrode recording, brain stimulation, and psychologic testing and have a computer system with high-speed graphics capability for the recording and processing of electrophysiologic and behavior data. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted, species-typical behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior.

Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, ethology, psychology, ecology, paleobiology, and systematics. The laboratory is located at the NIH Animal Center near Poolesville, MD.

Clinical and Research Branches
Richard J. Wyatt, M.D.
Llewellen B. Bigelow, M.D.

This program, located at Saint Elizabeths Hospital, conducts intramural research on special mental health problems, such as psychopharmacology, neuropharmacology, neuroanatomy, sleep, memory, normal and abnormal human behavior, and geriatric psychiatry. Clinical evaluations, treatment, and followup are an integral part of all research protocols.

Adult Psychiatry Branch—
Richard J. Wyatt, M.D.

This clinical research laboratory capitalizes on many disciplines in its effort to understand and treat schizophrenia, the psychiatric problems of the elderly, central nervous system regeneration, memory, sleep, and its disorders. The laboratory is set up so that small groups of young scientists may employ biochemical, structural, anatomic, pharmacologic, physiologic, and psychologic techniques in their work with these basic science and clinical problems.

The major focus of the branch's research takes place on three inpatient research wards. Llewellen B. Bigelow, M.D., is the clinical director. There is substantial opportunity to examine drug-free patients and to use pharmacologic probes to discern different patient groups. Three 12-bed research wards housed in the William A. White Building are devoted to schizophrenia and neuropsychiatric research. There is also an outpatient department. In addition, many of the 1,800 inpatients at Saint Elizabeths Hospital participate in research programs.

- Group on Mass Spectrometry—
  Farouk Karoum, Ph.D.

The laboratory operates two quadruple mass spectrometers which are primarily used in clinical studies to measure neurotransmitters and their metabolites. A major current interest is measuring phenylethylamine (PEA), and endogenous amphetamine-like compound which has been suggested to be elevated in the urine of some paranoid schizophrenic patients.

- Clinical Psychopharmacology Section—
  Richard J. Wyatt, M.D.

This section primarily studies the pharmacology of psychotropic medications and patients' response to them. Clinical and animal samples are routinely assayed for determining the pharmacokinetics and pharmacodynamics of these agents.

- Section on Aging
  David Shore, Ph.D., and
  Dilip Jeste, M.D.

This group is actively carrying out clinical studies in geriatric patients with psychiatric illnesses. These include depression, alcoholism, Alzheimer's disease, and tardive dyskinesia. Current studies in depression are attempting to look at pharmacokinetics and to evaluate psychotherapy versus tricyclic antidepressants in a geriatric population. Alcohol studies are being carried out in conjunction with scientists in the Alcohol Institute, in an attempt to understand psychologic and physiologic changes that occur with chronic drug abuse in older individuals. A principal hypothesis about the etiology of Alzheimer's disease is that aluminum deposits accumulate on the DNA of the brains of patients with Alzheimer's disease. This group is currently carrying out a project to determine whether or not decreasing aluminum in the body of patients with Alzheimer's disease has any effect on the course of this illness. Tardive dyskinesia is a principal and serious side effect of the clinical use of neuroleptic drugs. It is far more common in older patients than younger ones. This group is currently trying to determine both the etiology and how we can best prevent tardive dyskinesia in patients who must be on these drugs for long periods of time.

- Basic Neurosciences Section—
  William J. Freed, M.D., and
  Luis de Medinaceli, M.D.

This group emphasizes the exploitation

of brain grafting techniques to correct lesion-induced behavioral deficits. Currently under study are the characteristics of the brain as a site of transplantation and the potential of brain grafts to effect functional reconstitution. A major success has been in grafting adrenal medulla or substantia nigrato the caudate nucleus, thereby correcting the rotational behavior that develops following unilateral substantia nigra lesions. Destruction of the substantia nigra has been considered by many to be an animal model of Parkinson's disease, and this group is applying these techniques to rats and monkeys in order to develop brain grafting within this model. Other related interests involve the transplantation of endocrine tissue and retinae to the rat brain.

Although fiber sprouting is always observed following peripheral nerve injury, the functional consequences of such injury are variable, and in mammals, functional recovery is frequently slow and incomplete. This group is interested in developing new approaches to peripheral nerve repair, in order to improve the rate and degree of functional recuperation, and to better understand the mechanisms involved in promotion and obstruction of peripheral nerve regeneration in mammals.

- Neuropsychiatry Section—
  Daniel R. Weinberger, M.D., and
  Janice R. Stevens, M.D.

This group is investigating the relationship of behavior and psychopathology to neuroanatomic and neurochemical alterations in the brains of patients with neuropsychiatric disorders, principally schizophrenia. In living subjects, the emphasis is on linking brain structure, metabolism, and function to develop more meaningful dimensions of psychiatric syndromes. Powerful new techniques that are currently utilized include computed tomography (CT), xenon-133 regional cerebral blood flow, and positron emission tomography (PET), and brain electrical activity mapping (BEAM).

- Section on Schizophrenia—
  Joel E. Kleinman, M.D.

A large human brain bank is the focus of postmortem studies that are evaluating neurochemical, immunologic, and virologic hypotheses of neuropsychiatric illness. Current projects include qualitative and quantitative neuroanatomy, immunocytochemistry, and studies of biogenic amine, peptide, and receptor neurochemistry.

Laboratory of Preclinical Pharmacology—
Erminio Costa, M.D.

Scientific efforts of this laboratory are directed toward the elucidation of neuronal control mechanisms that mediate responses of drugs affecting neuronal function. The laboratory is organized into one group and four section.

- Group on High-Pressure Liquid Chromatography—James Meek, Ph.D.

New methods are developed to investigate drug effects on renovation rates of brain stores of monoamines and neuropeptides.

- Section on Biochemical Pharmacology—Norton Neff, Ph.D.

This section conducts investigations directed at the identification of control mechanisms for enzymes that regulate the dynamics of putative brain neurotransmitters and the determination of drug actions on the regulation of turnover rate of brain monoamines using mass fragmentography.

- Section on Neuropeptides—
  Hsiu-Ying T. Yang, Ph.D.

Studies of neuropeptides operative in the regulation of pain threshold are carried out with target on the molecular mechanisms of tolerance and dependence to morphine. Enzymes involved in neuropeptide processing and inactivation are characterized and purified. cDNA probes for neuropeptide precursors are prepared.

- Section on Neuroendocrinology—
  Alessandro Guidotti, M.D.

Efforts are directed towards the study of: (1) the role of protein phosphorylation in gene expression, and 2) the role of endogenous opiate peptides and GABAergic system of chromaffin cells in the modulation of catecholamine secretion elicited by splanchnic nerve stimulation. The mechanism of action of benzodiazepines and the role of GABAergic mechanisms in the neurobiology of anxiety are also a main research focus of this section.

- Section on Molecular Neurobiology—Erminio Costa M.D.

The molecular mechanisms operative in the function of transmitter receptors is being studied using monoclonal antibodies to various receptor subunits to obtain cDNA probes. The turnover rate of neuropeptides *in vivo* is evaluated using hybridizatoin techniques to measure specific mRNA content of various brain nuclei. Autacoids for drug receptors are isolated, purified and studied to develop biochemical markers for psychoses.

National Institute of Neurological and Communicative Disorders and Stroke

Murray Goldstein, D.O., M.P.H.,
Director
Irwin V. Kopin, M.D.
Director, Intramural Program
Richard L. Irwin, Ph.D.
Associate Director for Laboratories
Paul L. Kornblith, M.D.
Acting Clinical Director

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) provides broad opportunities for post-doctoral training in the basic and clinical neurosciences. Laboratories and clinics operated by the Institute are located principally on the main NIH campus in Bethesda, Maryland. Limited training opportunities also exist at NINCDS facilities in Frederick, Maryland, Woods Hole, Massachusetts, and on Guam. Most medical staff fellows participate in clinical neurosciences research in Institute laboratories and clinics, and have responsibility for the care of patients admitted for study. Some fellows primarily engage in basic laboratory investigations. All work is conducted under the preceptorship of a senior staff member and fellows are encouraged to avail themselves of an active program of teaching seminars, invited lectureships, and ward rounds.

Appointments in Clinical Research

Medical staff fellow positions for the National Institute of Neurological and Communicative Disorders and Strokes (NINCDS) are available in medical and surgical neurology, experimental therapeutics, infectious diseases, neuroimmunology, neuroepidemiology, and developmental and metabolic neurology. Fellows are usually appointed for 2 years, with the possibility of extended affiliation.

Major components of this program include patient care responsibilities on NINCDS wards, involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Medical staff fellows have the opportunity to work closely with senior investigators, to attend on-site courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NINCDS research emphases.

Candidates requiring further information about NINCDS clinical positions for medical staff fellows should write to Irwin V. Kopin, M.D., Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 10, Room 5N214, National Institutes of Health, Bethesda, Maryland 20205.

Appointments in Laboratory Research

NINCDS medical staff fellow positions are available in neurochemistry, neurophysiology, nueropathology, neurootolaryngology, biophysics, molecular biology, biology, molecular genetics, and other areas of fundamental neurosciences investigation. Appointments are for 2 years, with the possibility of extended affiliation.

Areas of study are developed by each fellow in conjunction with a preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the fellow is assigned. Independence and originality of approach are encouraged.

Medical staff fellows have the opportunity to work closely with a large and diverse group of senior investigators, to participate in on-site courses and conferences, and to employ advanced neuroscience technology in the conduct of their research.

For further information on the NINCDS Medical Staff Fellowship Program, write to Irwin V. Kopin, M.D., Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 10, Room 5N214, National Institutes of Health, Bethesda, Maryland 20205.

Medical Staff Fellows in Epidemiology

Intramural Research Program—
Thomas N. Chase, M.D.

- Section on Neuroepidemiology—
  Bruce S. Schoenberg, M.D., Dr.P.H., and Roswell Eldridge, M.D.

This section conducts national and international studies concerning the patterns of neurologic disorders in human populations. Both environmental and genetic factors in disease etiology are considered. The medical staff fellow receives training in the utilization of neuroepidemiologic and neurogenetic techniques to the solution of practical problems in clinical neurology and neurosurgery. Although the section's program involves the application of epidemiologic methods to the study of any disorder of the nervous system, current research concentrates on cerebrovascular disease, brain tumors (including neurogibromatosis), dementia, cerebral palsy, torsion dystonias, multiple sclerosis, parkinsonism, and racial differentials in the occurrence of neurologic disease.

Clinical Branches

Clinical Neurosciences Branch—
Paul Fedio, Ph.D., Acting

Various clinical and electroencephalographic (EEG) aspects of seizure disorders are investigated, with emphasis on diagnosis and localizaton. Cerebral evoked response techniques are also applied for clinical and research studies. Consultative EEG and cerebral evoked response examinations are provided to neurologic and psychiatric patients within the NIH. Basic investigations are focused on pathophysiologic and pharmacologic aspects, utilizing a kindling model of epilepsy. The appointment of medical staff fellows is for 2 years, and preference is given to applicants with experience in clinical neurology and electrophysiology.

Developmental and Metabolic Neurology Branch—
Roscoe O. Brady, M.D.

- Section on Enzymology and Genetics—
  Roscoe O. Brady, M.D.

Principal research efforts concern the pathologic biochemistry, diagnosis, carrier identification, and genetic counseling related to inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, Krabbe's disease, and Tay-Sachs disease, along with the development of enzyme purification procedures for replacement therapy trials. Other studies include alterations of complex lipid metabolism in neoplastic cells and investigations of genetic mutations of cholesterol metabolism in experimental animals.

- Section on Neurochemical Methodology—
  Andrew E. Gal, Ph.D.

This section is involved in the preparation of widely useful substrates for the facile diagnosis of metabolic disorders, the development of ultramicroanalytic procedures for monitoring the effects of enzyme replacement therapy, and the synthesis of novel lipids and lipid analogs for metabolic studies in normal and pathologic tissues.

- Section on Myelin and Brain Development—
  Richard H. Quarles, Ph.D.

Research is primarily concerned with the composition and metabolism of myelin components in the developing nervous system and an examination of abnormalities of their structure and function in demyelinating conditions such as multiple sclerosis and in peripheral neuropathies.

- Section on Molecular and Medial Genetics—
  John A. Barranger, M.D., Ph.D., Acting

The section conducts research on the biochemistry and molecular genetics of inherited disorders of metabolism. Work is focuses on basic studies of lysosomal storage disorders. Projects include cDNA and genomic cloning of the genes for lysosmal enzymes, gene transfer, expression of genes in bacterial and mammalian cell genetic recombinants, gene assignment, DNA restriction fragment polymorphism, and the development of diagnostic methods in a variety of mutants.

- Section on Membrane Biochemistry—
  Peter H. Fishman, Ph.D.

Research is directed towards the biosynthesis, organization, and function of cell membranes including transmembrane signaling of receptor-mediated information, regulation of membrane enzymes, biogenesis of membrane components, and topologic organization of cell-surface respectors.

- Section on Clinical Investigations and Therapeutics—

Basic research is conducted on the biochemistry of lysosomal glycoprotein enzymes. Structure, biosynthesis, subcellular localization, and properties of the enzymes responsible for their assembly into lysosomal membranes, *in vivo* activity, and turnover are examined. Applied research deals with the clinical diagnosis and study of the lysosomal storage disorders and clinical trials of novel therapies.

Experimental Therapeutics Branch—
Thomas N. Chase, M.D.,

- Section on Pharmacology—
  Thomas N. Chase, M.D.

This section conducts an integrated program of preclinical and clinical studies directed towards the rational development of improved therapies for extrapyramidal and dementing disorders. Current investigations focus on the pharmacology of central transmitter systems; biochemical and cerebral imaging (positron emission tomography) approaches are used to related neurologic symptoms to dysfunction of specific classical or peptidergic systems. Pharmaceutical testing is carried out in animal models and in research patients.

- Section on Clinical Epilepsy—
  Roger J. Porter, M.D.

The major effort of this section is the intensive monitoring of patients with uncontrolled seizures by videotape recordings and telemetered electroencephalography, the study of the metabolism and efficacy of various antiepileptic agents, and studies on the usefulness of new scanning procedures, such as positron emission tomography.

- Section on Biochemical Neuropharmacology—John Kebabian, Ph.D.

Research is conducted on the biochemical properties of synaptic receptor mechanisms in the central nervous system (CNS) and drug-induced modification of receptor activity. Particular attention is directed towards the D-1 and D-2 dopamine receptors.

- Section on Physiological Neuropharmacology—
  Judith Walters, Ph.D.

This section investigates neurophysiological aspects of neuronal function and drug action in the CNS, especially in the basal ganglia and substantia nigra. Current studies include investigation of the consequences of dopamine receptor stimulation, the modulatory interactions of dopamine with other neurotransmitters and dopamine-GABA-peptide interrelationships in the basal ganglia. Single unit recording and iontophoretic techniques are utilized in *in vivo* and *in vitro* preparations in conjunction with supportive biochemical procedures.

- Unit on Neuroendocrinology—
  Thomas O'Donohue, Ph.D.

The unit conducts preclinical investigations of neurotransmitter biochemistry which will eventually lead toward a better understanding of neurological disease and the development of new pharmacological therapeutic agents. Particular emphasis is placed on the identification of important neuropeptide systems in the central nervous system. Studies focus on anatomy, biosynthetic processes, receptors, and physiological action of these new neurotransmitter systems.

Infectious Diseases Branch—
John Sever, M.D., Ph.D.

- Section on Immunochemistry and Clinical Investigations—
  Sidney Houff, M.D.

The pathogenesis of multiple sclerosis, Epstein-Barr virus infections, amyotrophic lateral sclerosis, and progressive multifocal leukoencephalopathy is under study. Persistent perinatal infections are also being investigated. The role of viruses and cellular immune responses in patients and experimental animals is being tested. Clinical work is done on abnormal antibody and cellular immune reactions in these patients.

- Marinos C. Dalakas, M.D.

The immune and viral pathogenesis of neuromuscular disorders is being investigated and clinical therapeutic trials are conducted. The role of viruses and immune responses in patients with Gullain-Barre syndrome, chronic relapsing polyneuropathies, polymyositis/dermatomyositis, post-poliomyelitis syndrome, ALS, and Reye's syndrome is being studied. The mechanism of amyloid deposits and the specific immune nature of paraproteinemia is being investigated in patients with amyloid and paraproteinemic polyneuropathies. Studies are also conducted in patients with amyotrophic lateral sclerosis (ALS) using the PET scan to investigate changes in the cerebral metabolic rate for glucose in the motor cortex, and experimental therapeutics trials with new immunomodulating agents are explored. Clinical research in these areas is combined with muscle and nerve biopsy techniques, muscle histochemistry, immunocytochemistry, and characterization of function and markers of lymphocyte subsets.

- Section on Neurovirology—
  Maneth Gravell, Ph.D.

This section is involved in research on viruses as causes of tumors of the brain, PML, MS, Reye's syndrome, and cerebellar disease with infectious mononucleosis (Epstein-Barr virus), as well as experimental models of persistent virus infections. Methods include tissue culture, cocultivation, new tests for cellular immunity, and antibody determinations.

- Section on Experimental Pathology—
  W.T. London, D.V.M.

Studies of perinatal infections that cause birth defects and persistent central nervous system infections are conducted in monkeys and small laboratory animals. Papovaviruses, cytomegaloviruses, toxoplasmosis, and herpes viruses are being used. Methods for direction, treatment, and prevention are being developed. Persistent infections with polyomaviruses, progressive multifocal leukoencephalopathy, and glioblastomas are under investigation.

One medical staff fellow is appointed annually for 2 years. The individual participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as fellows for a 2-or 3-year period. These individuals perform basic research relevant to neurologic disease.

Surgical Neurology Branch—
Paul L. Kornblith, M.D.

This branch investigates and treats clinical problems of disordered neuronal and glial proliferation and differentiation. A major part of the program is devoted to the study of intracranial tumors including pituitary tumors. Problems of both central and peripheral neuronal and glial regeneration are also under study. Clinical research in these areas is combined with basic techniques of cell biology, tissue culture, biochemistry, immunology, pharmacology, and light and electron-microscopic histology to provide for an in-depth exploration and, ultimately, new approaches to these problems.

Experimental neuropathology and neuroimmunology is emphasized in a program which includes clinical diagnostic neuropathology. Biochemistry, morphology, and immunochemistry of neoplasms are studies as means of improving detection and treatment and as clonal models of their nonneoplastic counterparts in nervous and lymphoid tissues.

Studies are being carried out on cell-mediated immune mechanisms in human brain tumor patients, including delineation of the effectiveness of various forms of cell-mediated immunity to contribute to the destruction of brain tumors, examination of the ability of brain tumors to elicit cellular immune responses both *in vivo* and in model systems *in vitro*, and exploration of possible modes of altering brain tumor cells so as to increase their immunogenicity. This work is complemented by studies in animal models on basic mechanisms of cell-mediated immune lysis of tumor cells.

The medical staff fellow participates in the care of patients on the various protocols of the Surgical Neurology Branch as well as consultative care of patients with neurosurgical problems in all the NIH institutes. The fellow receives training in the diagnostic and operative techniques of surgical neurology with special emphasis on microneurosurgery both in the animal laboratory and in the operating room. In addition, there will be opportunity for work in the laboratory with training in a wide range of cell biology techniques, with special emphasis on tissue culture, immunoneurology, and electron microscopy. Experimental surgery and other therapy in animal models as it relates to the clinical problems under study will also be performed. The fellow also works in collaboration with senior scientists or independently in specific laboratory areas as his or her experience and interest dictates.

- Section on Neuroradiology and Computed Tomography—
  Giovanni Di Chiro, M.D.

Work in this section currently focuses on the latest applications of transmission computed tomography and its further development as a noninvasive method for morphologic and functional studies of the nervous system. The section is also very actively involved in emission computed tomography using positron emitting radionuclides (positron emission tomography). Particular emphasis is placed on correlative studies between transmission and emission-computed tomography.

Neuroimmunology Branch—
Dale E. McFarlin, M.D.

Research is performed in the following areas: characterization of the immune response to viral agents, such as measles which causes chronic infection in patients with neurologic diseases; study of certain animal models; study of model autoimmune diseases such as experimental allergic encephalomyelitis; assessment of the immune response to components of membranes in the peripheral nervous system and CNS; evaluation of immune function in patients with chronic neurologic disorders of unknown etiology, such as multiple sclerosis and Parkinsonism, which may be related to either a persistent infection of the nervous system or immunopathologic mechanisms; assessment of the immune reactivity in human diseases believed to have an autoimmune etiology such as myasthenia gravis; and assessment of new therapeutic agents which alter the immune response.

Two medical staff fellows are appointed annually for 2 years. These individuals participate in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as research associates for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Basic Research Laboratories

Laboratory of Central Nervous System Studies—
D. Carleton Gajdusek, M.D.

This laboratory is engaged in two studies: (1) The medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior, and learning. High incidence and other unusual foci of chronic CNS diseases, asthma, parasitic and viral diseases, congenital metabolic defects, atypical patterns of puberty and aging, toxic and deficiency syndromes, and unusual behavior syndromes, where isolation or cultural stereotypy may contribute to epidemiologic solutions, are under study. Aspects of learning and socialization in primitive disappearing cultures are documented using still and cinema photography and sound recording. New methods of handling such data for research are developed. (2) The slow, latent, and temperate virus infections, with particular attention to chronic degenerative neurologic disease and basic virologic and immunologic studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by unconventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie, and mink encephalopathy) that form a new group of microorganisms tentatively called "viruses," although they contain much smaller genetic information and possess very different properties than any other group of viral agents. The biological and molecular characterization of these unconventional viruses is the major focus of the work. Aging of the brain, Alzheimer's, Pick's, Parkinson's, and Huntington's diseases, multiple sclerosis, amyotrophic lateral sclerosis, chronic epilepsies, and other diseases are intensively studied in microbiological, immunologic, genetic, and biochemical laboratories and clinics and in foci of high incidence throughout the world.

Within this framework intensive investigation of epidemic hemorrhagic fever/hemorrhagic fever with renal syndrome is being conducted on a worldwide basis on the isolation and characterization of the virus, its molecular nature and immunogenetics, its seroepidemiology, and the documentation of mild forms of the disease in man.

Laboratory of Molecular Genetics—
Robert A. Lazzarini, Ph.D.

This laboratory investigates the component molecular events that participate in the replication and expression of the genetic materials of mammalian cells and their viruses. Genetic, biochemical, and recombinant DNA techniques are employed in the study of the replication and transcription of genes that ultimately lead to their expression as protein. These studies are directed toward a full understanding of the delicate interplay between the complementing genetic elements in normal cells, chimeric cells, and cells persistently infected with viruses.

- Molecular Virology Section—
  Robert A. Lazzarini, Ph.D.

This section studies aspects of virus-host interactions at the molecular level. These include viral penetration of host cells, viral replication, and the assembly of progeny particles. Particular attention is focused on the involvement of host factors in the replication of the viral genome and the relationship of these to viral host range, persistency, latency, and cytopathology.

- Recombinant Genetics Section—
  Robert A. Lazzarini, Ph.D.

Studies are under way of eukaryotic gene expression and genetic complementation in cultured mammalian cells. These studies employ both recombinant DNA and classical biochemical techniques to probe the control of gene transcription, the processing of primary transcripts, and eventual expression of these RNA's as proteins.

- Neural and Molecular Ultrastructure Section—
  Monique Dubois-Dalcq, M.D.

Studies are under way on: (1) growth factors and purification methods of rodent and human nerve cells, and (2) how nerve cells are affected by neurotropic viruses. More specifically, virus tropism and assembly is studied in nerve cells as well as susceptible cells. Methods employed consist of immunolabeling for light and electron microscopy as well as microinjection of monoclonal antibodies to viral proteins into living cells. (3) The emergence and assembly of myelin proteins during nervous system development using immunocytochemical methods are examined. Similar methods are used to study the alternations in myelin proteins in diseased nerves.

Laboratory of Neural Control—
Robert E. Burke, M.D.

Fundamental research is conducted on the properties of mammalian nerve cells and on the organization of the mammalian CNS with particular reference to studies of the control of movement. Current experimental studies involve three main areas: 1) the CNS control of spinal cord motorneurons and in turn the control exerted by these cells on the muscle fibers innervated by them, 2) the organization of information-processing systems in the spinal cord, and 3) the activity of motor cortex neurons and of individual peripheral afferents during normal movement in intact animals. Such studies utilize established as well as newly developed techniques for electrophysiologic recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The laboratory has facilities for the development of specialized experimental equipment and novel electrode designs suitable for chronic implantation, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

Laboratory of Neurochemistry—
Janet V. Passonneau, Ph.D.

Research is conducted on molecular events that underlie the normal functioning of the nervous system and derangements that occur in neurologic diseases.

- Section on Cellular Neurochemistry—
  Janet V. Passonneau, Ph.D.

Section is involved in studies on metabolism in neural tissues. Emphasis is placed on the microanalytical techniques used to measure metabolites in discrete regions of the brain or in single cells. In the retina the metabolic response of retinal layers to light and dark adaptation is studied, and Dr. Ralph Nelson investigates the light responses of individual cells by intracellular electrophysiological techniques. Other projects include the regional alterations of energy metabolites in ischemic brain, the role of guanine nucleotides in brain function, glycogen metabolism and protein synthesis.

- Section on Enzyme Chemistry—
  Wayne Albers, Ph.D.

This enzymatic mechanism of active Na^+ and K^+ transport is investigated. Other current projects involve g-aminobutyric acid metabolism, brain mitochondria, and membrane receptors.

- Section on Neuronal Development and Regeneration—
  Andrew Zalewski, M.D.

This section is attempting to elucidate the factors involved in nerve fiber regeneration, trophic nerve function, and selectivity and plasticity in the formation of neural connections. A variety of neurohistologic, histochemical transplantation, and immunologic techniques are being used in these studies.

Laboratory of Neuro-Otolaryngology—
Jorgen Fex, M.D., Ph.D.

Inner ear neuronal mechanisms are being studied in mammals. The long-range purpose of the project is to study the biochemistry, morphology, pharmacology, and physiology of inner ear neurons and cells and their interactions and to describe the mechanisms of these interactions. A second project concerns the synaptic transmission and neuronal connections of the mammalian cochlear nucleus. A multidisciplinary approach is being used for this project. A major, long-term program of this laboratory is to solve problems concerning hereditary deafness in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models.

Laboratory of Cerebral Vascular Neuropathology
Igor Klatzo, M.D.

The laboratory recognizes the scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomic sciences. Thus, investigations on mechanisms operative in various neuropathologic conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system.

- Section on Cerebrovascular Pathology—Igor Klatzo, M.D.

Research is conducted on various aspects of pathophysiology of cerebral ischemia and brain edema. Elucidation of the pathomechanisms involved is attempted by evaluation and correlation of various parameters, such as changes in blood flow, electrical impedance, water content, electrolytes, glucose metabolism, behavior of the blood-brain barrier, and morphological alterations in various models of ischemia and traumatic brain injury.

- Section on Neurocytobiology—
  Maria Spatz, M.D.

This section investigates the normal and pathological properties of cerebral endothelium which is the main substrate of the blood-brain barrier. The investigations include observations on transport mechanisms in endothelial cells, on their receptors, and on the effect of various substances in modifying barrier phenomena and the course of edema and ischemia.

Laboratory of Experimental Neuropathology—
Henry deF. Webster, M.D.

This laboratory studies cellular mechanisms of myelin formation, maintenance and breakdown with special emphasis on roles viruses may have in multiple sclerosis and other demyelinating diseases. Virological, immunocytochemical, immunological, biochemical and biophysical techniques are being used in current projects.

Laboratory of Neurobiology—
Thomas S. Reese, M.D.

Conducts structural research on the organization of the nervous system. Specific cell biological problems are synaptic tranmission, glial function, axoplasmic transport, organization of glial and neural membranes, and the intracellular sequestration of ions. The principal organizational problems investigated are the blood-brain barrier, and neural development and regeneration. Structural tools used are electronmicroscopy, X-ray spectroscopy, immunocytochemistry, cryotechniques, and computer processed imaging.

- Section on Functional Neuroanatomy—Thomas S. Reese, M.D.

This section is primarily concerned with studies on synaptic structure and function, redistribution of elements during neuronal activity and secretion, instrinsic membrane proteins and lipids, and neuronal cytoskeleton. Using modern electron optical and low temperature techniques, the structure of neural cells and membranes is investigated in close to molecular level of resolution.

- Section on Structural Plasticity—Milton W. Brightman, Ph.D.

The section is engaged in studies to delineate the conditions necessary for the placement, survival, regeneration, and function of transplanted neurons—both peripheral and central, to characterize further the tropism between central and peripheral neurons and to analyze the structural changes in astrocytic cell membranes during degeneration and regeneration.

Laboratory of Neurophysiology—
Jeffery L. Baker, M.D.

All of the laboratory's projects involve multi-disciplinary analysis of the physiological properties of vertebrate central neurons studied *in vitro*. The techniques utilized encompass many of those current in cellular neurobiology, including electrophysiology, immunohistochemistry, electronmicroscopy, flow cytometry and dissociated cell culture. A principal line of investigation is focused on the physiological properties of neurons cultured from different parts of the mammalian CNS, since monolayer cultures allow immediate accessibility to quantitative analysis of neuronal function at the cellular level. Using such a strategy, members of the laboratory are studying which properties are resident in different types of nerve cells, how these properties evolve during embryonic development, and what roles they play in intercellular communication. These studies are thus aimed at providing insight primarily into the question of what types of phenotypic properties are expressed by different CNS cells and secondarily into the related problem of how these properties differentiate the functions of one cell type from another. One long-term goal of the laboratory is a better understanding of the relationship between the activity of ion channels in neuronal membranes and the synthesis and secretion of specific transmitter substances.

Another area of considerable activity in the laboratory involves pharmacological experiments on the cellular mechanisms of actions of clinically important drugs like benzodiazepines, barbiturates, and convulsants using electrophysiological recording techniques (voltage-clamp and patch-clamp).

Laboratory of Molecular Biology—
Ernst Freese, Ph.D.

Developmental effects of mutations and drugs are examined. They are correlated to hereditary diseases and teratogenic effects.

- Section on Developmental Biology—Ernst Freese, Ph.D.

The control of cell differentiation is studied in bacteria and yeast using mutations, genetic engineering, and drugs. The developmental effects are examined in terms of metabolism and the control of nucleic acid, enzyme, wall, and membrane synthesis. The molecular changes of nucleic acid, proteins, and membranes are analyzed.

- Section on Molecular Neurobiology—

Studies are designed to further our understanding of the mechanisms by which individual cells respond to external signals. Cell surface receptors for hormones and neurotransmitters, in particular those whose function involve modulation of cAMP levels are investigated using the methods of biochemistry and biology.

Convulsive, Developmental, and Neuromuscular Disorders Program

Epilepsy Branch—

Roger J. Porter, M.D.

This branch develops and coordinates organized and directed research programs on a multi-institutional, geographic, or multidisciplinary basis through its support of five comprehensive programs, each serving a specific geographic area. It develops, conducts, and coordinates collaborative and directed research programs aimed at finding new or improved methods of diagnosis, treatment, and prevention of convulsive disorders. The clinical investigation of new antiepileptic drugs is a major concern. The branch fosters the synthesis, screening, and pharmacologic and metabolic investigation of antiepileptic drugs by collaborative efforts; conducts research on the metabolism of anticonvulsant drugs and the treatment of certain difficult seizure disorders according to rigid protocols within its own facilities; and fosters research in experimental models of epilepsy and improved patient treatment through the use of serum antiepileptic drug determinations.

The Clinical Center

John L. Decker, M.D.,
Director

Blood Bank Department—

Harvey G. Klein, M.D.

Staff Fellowship

The Blood Bank Department accepts applications for an American Medical Association accredited fellowship program in blood banking and immunohematology. The fellowship assignment is usually for 2 years. Vacancies do not necessarily occur each year. Board certification or eligibility in internal medicine, clinical pathology, or hematology is required.

The program offers training in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. The fellow receives broad experience in all aspects of blood banking, including clinical and laboratory immunohematology, apheresis techniques, tissue typing, donor recruitment, and blood component preparation and therapy. The fellow participates actively in the service and teaching functions of the Blood Bank.

Involvement in a clinical or basic research project is encouraged. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various institutes. Current programs include investigations into the various agents responsible for posttransfusion hepatitis, the effects of biologic incompatibilities on transfusion and transplantation, immunologic studies of drug-induced hemolytic anemias, and innovative uses of automated apheresis techniques.

Prospective applicants desiring more information should write to Richard J. Davey, M.D., Program Director, Blood Bank Department, Building 10A, Room 1E33, National Institutes of Health, Bethesda, Maryland 20205.

Clinical Pathology Department—

Ronald Elin, M.D., Ph.D.

The Clinical Pathology Department offers a broad spectrum of laboratory diagnostic services for intramural patient care for the institutes. The department is organized into three services: clinical chemistry, hematology, and microbiology. In addition, there is a close working relationship with the Information Systems Management Department. The Clinical Chemistry, Hematology, and Microbiology Services and the Information Systems Management Department, offer medical staff fellow positions, but not necessarily on a yearly basis.

- Clinical Chemistry—

The Clinical Chemistry Service provides all the chemical diagnostic tests on the patients in the Clinical Center, as well as for outpatient clinics. The senior staff is composed of five individuals with M.D. and/or Ph.D. degrees. Approximately 100,000 tests are performed per month by a technical staff of 42 medical technologists, chemists, technicians, and medical aides. The Clinical Chemistry Service collaborates in clinical research of a chemical nature and conducts extensive research and development in analytic methodology, automation, and computerization. Current interests within the service are the development of radioimmunoassays, adaptation of the calorimeter for laboratory testing, electrophoresis, factors affecting the reference range, instrument evaluation, and automated assay.

A medical staff fellow entering this 2-year program would receive in-depth training in the various aspects of clinical chemistry. The first year of the program would be devoted to a rotation through the clinical chemistry sections—STAT tests, electrophoresis, radioimmunoassay, urinalysis, special chemistry, and SMAC. In addition, emphasis would be placed on the correlation of laboratory data with the status of patients. The fellow would be encouraged to attend working patient rounds and to handle inquiries to the Clinical Chemistry Service from patient-care physicians. Also, during this first year, the fellow would have the opportunity to develop specific interests in investigative studies. During the second year of the program, the fellow would be encouraged to choose a research project for independent investigation under the supervision of a senior staff member or to participate in an ongoing research project.

Any candidate interested in the Medical Staff Fellow Program should write to Ronald J. Elin, M.D., Ph.D., Chief, Chemistry Service, Clinical Pathology Department, Building 10, Room 2C-407, National Institutes of Health, Bethesda, Maryland 20205.

- Hematology

The Hematology Service provides clinical and research experience in hematology. The service is responsible for the operation of the routine clinical hematology, coagulation, and special hematology laboratories. We have an active clinical and consultative service. The Hematology Service also has a research program directed at clinical and basic problems in hematology. Research of particular interest includes coagulation, thrombosis, platelet disorders, advances in morphologic interpretation of bone marrow material, purification and characterization of coagulation proteins, studies on platelet physiology and pathology, and the study of the role of carbohydrates in coagulation and platelet function. Other research endeavors include the use of immunologic and biochemical markers for hematopathologic diagnoses including flow cytometry and the development and testing of new procedures of analytic systems in the hematology laboratory.

The Hematology Service recruits medical staff fellows for a minimum of 2 years. Some fellows will spend at least 6 months doing primarily clinical work with patients in the Clinical Center. During this time, the fellow will also have the opportunity to develop a specific interest in investigative studies. Fellows will be encouraged to choose a problem for investigation which can be pursued with the guidance and supervision available in the Hematology Service, a joint project with an established investigator. Medical staff fellows whose primary interest is laboratory research are assigned to highly qualified physicians to provide an opportunity to improve their backgrounds for careers in basic medical research. During their tenure, these fellows will devote most of their time to laboratory research. The candidate who is chosen will be given an opportunity to choose an area of investigation, and a senior staff member will serve as his or her preceptor.

Any candidate interested in either program should write to Harvey R. Gralnick, M.D., Chief, Hematology Service, Clinical Pathology Department, Building 10, Room 2C-390, National Institutes of Health, Bethesda, Maryland 20205.

- Microbiology—

The Microbiology Service provides in-depth training in various aspects of clinical diagnostic microbiology, as well as the opportunity to participate in ongoing developmental research projects. Although the training program is primarily laboratory based, opportunity is considerable for interaction with the Infectious Disease Service and other patient-care physicians. The Microbiology Service is responsible for the isolation and identification of bacterial, mycobacterial, mycologic, and parasitic pathogens in Clinical Center patients. Determinations of antibiotic sensitivity and antibiotic levels are also performed, as well as a variety of clinical serologic procedures. No viral, chlamydial, or rickettsial work is currently performed in our laboratory. Present research activities include the use of computers for the organization and utilization of microbiology laboratory data, the development and assessment of a lysis-filtration and impedance system for blood culturing, and the evaluation of new methodologies for antibiotic sensitivity testing. A variety of clinicopathologic studies is also undertaken or could be initiated under senior staff supervision.

Persons interested in a medical staff fellowship position with the Microbiology Service should contact James D. MacLowry, M.D., Chief, Microbiology Service, Clinical Pathology Department, Building 10, Room 2C-385, National Institutes of Health, Bethesda, Maryland 20205.

- Laboratory Computer—

The Information Systems Management Department provides computer and statistical support for the patient-care and research programs of the Clinical Pathology Department. The service also conducts research on medical laboratory automation, computer-assisted interpretation of clinical laboratory measurements, variation in test results, and methods of quality control. The staff includes pathologists, programmers, and computer operators. In addition to its own minicomputer systems, the service makes extensive use of the NIH IBM 370 and DEC PDP-10 time-sharing computers. Investigators in the service utilize extensive machine-readable files of clinical and laboratory information pertaining to NIH patients.

A medical staff fellow works with the senior staff in applying computer and statistical techniques to problems of laboratory methods. Fellows are encouraged to develop independent or collaborative research projects. In addition, they may participate in teaching conferences of the Clinical Pathology Department. Appointments are for a period of 2 years and are not made yearly.

Interested candidates should write to Thomas L. Lewis, M.D., Associate Director for Information Systems Management, Clinical Center, Building 10, Room 2C-137, National Institutes of Health, Bethesda, Maryland 20205.

Critical Care Medicine Department—

Joseph E. Parrillo, M.D.

The Critical Care Medicine Department is offering 2- to 3-year fellowships in critical care medicine beginning in July

1985. To be eligible, a physician must have completed 3 years of residency in internal medicine, anesthesiology, or general surgery. The fellowship consists of a first year of clinical training in critical care medicine in the intensive care units at the National Institutes of Health and in the medical-surgical intensive care unit at the National Naval Medical Center (Bethesda Naval Hospital). The clinical training provides broad experience in the care of critically ill patients and in a wide variety of procedures necessary to critical care. The second year (and an optional third year for selected fellows) consists of an individually designed program in clinical investigation or basic laboratory research related to critical illnesses. The NIH Fellowship Program is designed to satisfy all the subspecialty Board requirements for critical care medicine. Critical Care Medicine Boards are planned for the first time in 1984.

The fellowship program is designed to provide excellent clinical training in the care of extraordinarily sick patients with multisystem organ dysfunction. Critical care physicians in the NIH ICU have primary responsibility for care of the patient. The critical care physicians work closely with referring physicians and call on multiple consultative services necessary to give full intensive care to these patients. The Critical Care Medicine Department consists of a senior staff that has subspecialty training in cardiology, pulmonary diseases, anesthesiology, infectious diseases, and critical care medicine. The staff performs most of the invasive procedures (Swan Ganz catheterization, cardiac catheterization, bronchoscopy, etc.) themselves in a specially constructed procedure/catheterization laboratory in the ICU. The ICU also has capability for computer processing and analysis, noninvasive (echocardiography, nuclear scanning) cardiac diagnostic studies, and pulmonary function studies.

The fellowship research training is designed to produce independent clinical investigators in the field of critical care medicine. The educational program includes weekly conferences on clinical critical care medicine and seminars regarding ongoing research programs in the department. Each fellow will have a senior staff member guiding the investigations. Ongoing research in the department includes the following: studies of hemodynamics and cardiovascular function in different forms of shock; the immunopathogenesis of septic shock; capillary leak syndromes; pulmonary functional abnormalities in shock lung; studies of immune cellular function in shock lung, asthma, and other forms of severe pulmonary disease; critical care of the immunocompromised host; and studies of immune cellular function and therapy of the acquired immune deficiency syndrome (AIDS).

For further information on the program, please contact Joseph E. Parrillo, M.D., Chief, Critical Care Medicine Department, Building 10, Room 10D48, National Institutes of Health, Bethesda, Maryland 20205.

Diagnostic Radiology Department—

John L. Doppman, M.D.

Staff radiologists are selected each year from among those applicants who have completed their residencies in diagnostic roentgenology. Such appointments are made for a period of 2 years, with opportunity for reappointment.

The department is well equipped to provide the routine and special diagnostic radiographic examinations needed by the 50,000-55,000 patients seen each year. Ultrasound and computed tomography play an increasingly important role in the diagnostic and research activities in the department. The preselection of patients for admission to NIH ensures a challenging and stimulating gamut of diagnostic problems.

Thirteen radiologists comprise the professional staff, and an adequate supporting staff is provided.

Facilities are available for collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

Nuclear Medicine Department—

Steven M. Larson, M.D.

One medical staff fellow is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in nuclear medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved internal medicine, radiology, or clinical pathology is recommended to meet the requirements for certification by the American Board of Nuclear Medicine.

Residency Training

The American Medical Association has approved the department for a 2-year residency training program in nuclear medicine. Qualifications for trainees include at least 2 years of prior training in radiology, pathology, or internal medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital or the Maryland University Hospital.

The department consists of three sections: The Diagnostic/Therapeutics Section, The Applied Physics Section, and the Radiopharmaceutical Chemistry Section.

The Diagnostic/Therapeutic Section provides clinical and investigative service to the physicians of the various institutes working within the Clinical Center. Rectilinear scanners and gamma cameras are the basic imaging devices. Within this section, the Positron Emission Tomography group provides positron imaging capability for the study of a broad range of conditions. Currently the emphasis has been on brain glucose metabolism in a variety of disease states and in normal conditions. This section is staffed by physicians and technicians who have the responsibility for clinical research imaging.

The radiopharmaceutical chemistry section has responsibility for the cyclotron production of positron-chemistry radiopharmaceuticals and also includes a radiopharmacy group, with broad responsibility for assuring the radiopharmaceutical purity and quality of all radioisotopes used for tumor use, throughout NIH.

The Applied Physics Section works toward the development of new data processing techniques. Computers for processing nuclear medicine data are located within the section. Department professionals are encouraged to interact with members of the various institutes to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases. The department also provides consultations and support for the use of radionuclides in diagnosis and research.

Division of Computer Research and Technology

Arnold W. Pratt, M.D.,
Director

The Laboratory of Applied Studies, DCRT, offers 2-to 3-year medical staff fellowship positions to physicians with additional training in physical science or engineering (including mathematics through differential equations), 2 years experience in computer programming, and at least 1 year of residency (internship).

Laboratory of Applied Studies—
James J. Bailey, M.D.

This laboratory engages in independent and collaborataive research on innovative applications of mathematics, computer science, and engineering to problems of basic biology and clinical medicine. The senior staff includes mathematicians, physicians, electronics engineers, and computer systems analysts; and facilities include access to micro-, mini-, and main frame computer systems (i.e. NIH IBM 370 and DEC-10 time sharing systems).

The fellow will collaborate with clinicians or bench lab scientists in one or more of such current projects as: electron/X-ray micro-analysis of biological specimens, ventilation/perfusion relationships in pulmonary scintigraphy, clinical use of functional images in radionuclide renography, pulmonary pathophysiology during exercise, electrophysiologic responses to cardiotoxic drugs and infective myocarditis, and use of evoked potentials to evaluate critically ill patients. The fellow will be guided by the senior staff, especially in such areas as: modeling of physiologic processes, (e.g. transport, reaction, diffusion, and receptor binding kinetics), mathematical methodology, signal analysis, image processing, and computer automation.

Interested candidates should contact: James J. Bailey, M.D., DCRT, Building 12A, Room 2041, National Institutes of Health, Bethesda, Maryland 20205.

Part Four

Academic Programs Available to Medical Staff Fellows

Among the academic programs open to an NIH medical staff fellow are: evening courses provided by the Foundation for Advanced Education in the Sciences, Inc. (FAES); formal seminars under the direction of NIH staff; combined clinical staff conferences; formal lectures; and symposia. The "NIH Calendar of Events" lists 40 to 50 programs each week. Other events of interest are held at universities and institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by the Graduate Program of the FAES, established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science. The foundation is an independent organization whose tuition and fees can be paid by a Federal employer. The FAES also operates the NIH bookstore, which supplies textbooks and other reading material for the convenience of NIH staff.

Courses are offered in two semesters, fall and spring. They are offered at the undergraduate and graduate levels under the programs of several departments of instruction: behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages, and general studies. The FAES and the Clinical Center sponsor board review courses in medicine and pediatrics. Subspecialty courses are offered for board review in endocrinology, hematology, and oncology. Further inquiries regarding the Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education in the Sciences, Inc., National Institutes of Health, Bethesda, Maryland 20205.

Seminars

An NIH program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent investigators and gives them the additional opportunity to master selected topics not adequately covered during college or graduate schooling. These seminars are now administered by the FAES, in conjunction with the evening courses. The program accommodates medical staff fellows involved in clinical or basic research and other properly qualified persons.

A number of tutorial seminars are generally made available each academic year in each of the following categories: biochemistry and genetics, cell biology, immunology, and physiology.

Weekly seminars run from September through January and from February through May. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of an expert in the field. In preparation for these, the medical staff fellow does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate institutes engaged in clinical research, the Clinical Center sponsors at least one monthly combined clinical staff conference for 8 months of the year. Each conference is conducted by one of the institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff and serve to keep individual investigators abreast of current emphasis in all clinical research.

Topics Presented in the 1983-84 Series Were:

October 4, 1983	Neal Cutler, M.D.	Brain Imaging, Aging, and Dementia
October 13, 1983	Ronald Wilder, M.D.	Rheumatoid Arthritis
November 1, 1983	Thomas Waldmann	Molecular Genetic Analysis of Human Lymphoid Neoplasm: Immunoglobulin Genes and the c-Myc Oncogene
December 9, 1983	Curtis Harris, M.D.	Tumor Promotion in Human Cancer
December 20, 1983	Joel Moss, M.D.	Cyclic Nucleotides: Targets of Bacterial Toxins in Disease
January 10, 1984	George Chrousos, M.D.	Clinical Applications of Corticotropin Releasing Factor
January 24, 1984	Charles Myers, M.D.	Drug Resistance in Cancer
February 14, 1984	Bryan Brewer, M.D.	The Role of HDL and the Development of Premature Cardiovascular Disease
May 29, 1984	Stephen Straus, M.D.	The Biology, Treatment and Prevention of Mucocutaneous Herpes Simplex Infections

Several formal lectures are presented annually. **The National Institutes of Health Lecture Series** was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the scientific directors of the institutes. Dr. Joan A. Steitz of Yale University gave the most recent NIH lecture in November, 1982 on "Autoantibodies as Probes for Small Ribonucleoproteins from Eucaryotes."

The **R. E. Dyer Lectureship** was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942-50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science. Dr. Robert C. Gallo of the National Cancer Institute presented the 1983 Dyer lecture on "Human Tumor Viruses: The Search for Some is Over." Among other distinguished speakers have been Nobel laureates Dr. Howard M. Temin, who spoke on "The Replication and Possible Origin of RNA Viruses with a DNA Polymerase," and Dr. D. Carleton Gajdusek, who discussed his work on kuru.

The **G. Burroughs Mider Lectureship** was established in 1968 by the scientific directors to honor Dr. Mider for his distinguished service to NIH. On advice of the scientific directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Recent Mider Lectures:

1982	William E. Paul, M.D.	Living with Lymphocytes, or B Lymphocytes and How They Grow
1981	Louis Sokoloff, M.D.	Metabolic Mapping of Local Functional Activity in the Central Nervous System
1980	Thomas Waldmann, M.D.	The Control of the Immune Response Regulatory Cellular Interactions and the Control of Lymphocyte Differentiation
1979	Martha Vaughan, M.D.	Regulation of Cyclic Nucleotide Metabolism
1978	Jesse Roth, M.D.	Receptor Disorders in Man
1977	Philip Leder. M.D.	A Close and Surprising Look at the Mammalian Genome
1977	Maxine F. Singer, Ph.D.	Monkey Business: Sequences in the Monkey Genome and Their Interaction with Simian Virus 40 DNA
1975	Karl A. Piez, Ph.D.	Collagen: Its Chemistry, Structure and Function
1974	Elizabeth F. Neufeld, Ph.D.	Inherited Lysosomal Disorders Studies in Cell Culture

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These, and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Uniformed Services University of the Health Services at the National Naval Medical Center, offer exceptional educational opportunities. Some medical staff fellows augment their experience at NIH with studies at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located on the first floor of the Clinical Center) is an open-stack, self-service library with a collection of some 272,000 volumes of medical and scientific books and journals. Some 2,000 new books and 3,700 journal subscriptions are received annually. An integral part of the research needs of the NIH staff, the NIH library's major subject areas include medicine, health sciences, chemistry, physiology, biology, physics and the peripheral areas of economics, education, legislation, and social sciences. A full range of services is provided NIH employees, including library copy service, manual and on-line bibliographic service, interlibrary loan, advisory consultation for literature needs, and a translating service.

The National Library of Medicine (NLM) is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 3 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service. Access to the library's computerized data base of journal references (MEDLINE) is available both at NLM and at the NIH library.

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NIH Publication No. 84-213
Revised April 1984

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